

EXPRESS MAIL NO. EL520287332US
C-3091/4 US

1

**NOVEL BENZOTHIOPINES HAVING ACTIVITY AS INHIBITORS
OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE**

5 This application is a continuation-in-part
application of U.S. Application Serial No. 09/816,065,
filed March 11, 1997, which claims the benefit of
priority of U.S. Provisional Application Serial No.
60/013,119, filed March 11, 1996. This application is
also a continuation-in-part application of U.S.
10 Application Serial No. 09/831,284, filed March 31,
1997, which is a continuation of U.S. Application
Serial No. 08/517,051, filed August 21, 1995, which is
a continuation-in-part application of U.S. Application
Serial No. 08/305,526, filed September 12, 1994. This
15 application also claims priority from U.S. Provisional
Application Serial No. 60/068,170 filed December 19,
1997.

BACKGROUND OF THE INVENTION

20

Field of the Invention

The present invention relates to novel
benzothiepins, derivatives and analogs thereof,
pharmaceutical compositions containing them, and their
25 use in medicine, particularly in the prophylaxis and
treatment of hyperlipidemic conditions such as is
associated with atherosclerosis or
hypercholesterolemia, in mammals.

30

Description of Related Art

It is well-settled that hyperlipidemic conditions
associated with elevated concentrations of total
cholesterol and low-density lipoprotein cholesterol are
major risk factors for coronary heart disease and
35 particularly atherosclerosis. Interfering with the

SRL 6071
(C-3021/2)

2

circulation of bile acids within the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction
5 leads to an improvement in the disease state of atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et Biophysica Acta, 1210 (1994) 255-287 discusses the
10 biochemistry, physiology and known active agents surrounding bile acids and cholesterol.

Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans by Heubi, J.E., et
15 al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", Gastroenterology, 1982:83:804-11.

In fact, cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their
20 normal enterohepatic circulation (Reihner, E. et al, in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein receptor expression in gallstone patients", Journal of
25 Lipid Research, Volume 31, 1990, 2219-2226 and Suckling et al, "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", Atherosclerosis, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver
30 using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

In another approach to the reduction of recirculation of bile acids, the ileal bile acid
35 transport system is a putative pharmaceutical target

SRL 6071
(C-3021/2)

3

for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 5 25, pp. 18035-18046, 1993).

In a series of patent applications, eg Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 10 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid 15 transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents.

In vitro bile acid transportinhibition is 20 disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds"

Selected benzothiepine are disclosed in world 25 patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

Other selected benzothiepine are known for use as hypolipaemic and hypocholesterolaemic agents, 30 especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

35 The above references show continuing efforts to

SRL 6071
(C-3021/2)

4

find safe, effective agents for the prophylaxis and treatment of hyperlipidemic diseases and their usefulness as hypocholesterolemic agents.

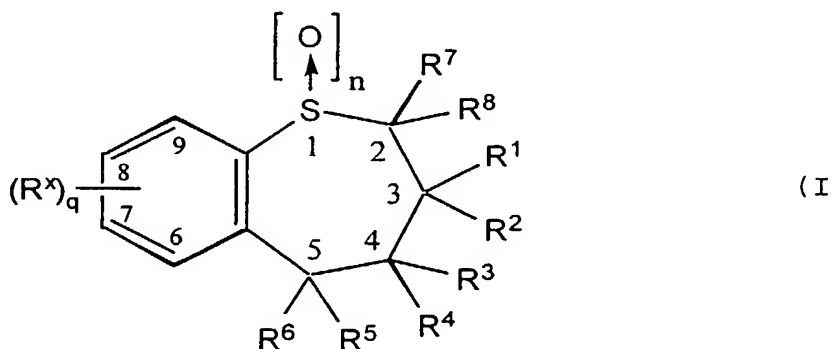
5 Additionally selected benzothiepinines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; 10 US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

The present invention furthers such efforts by providing novel benzothiepinines, pharmaceutical compositions, and methods of use therefor. 15

SUMMARY OF THE INVENTION

Accordingly, among its various aspects, the present invention provides compounds of formula (I):

20



wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

25 R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

SRL 6071
(C-3021/2)

5

dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

SRL 6071
(C-3021/2)

6

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9 , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

SRL 6071
(C-3021/2)

7

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle
5 can be further substituted with one or more substituent

groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary

10 heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O,

15 NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$,

$P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl,

20 alkylheteroarylalkyl, alkylheterocyclalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclalkyl, heteroarylalkyl, quaternary heterocyclalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and
25 carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 ,

$S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene,

30 carbohydrate, amino acid, peptide, or polypeptide, and

R^{13} , R^{14} , and R^{15} are optionally substituted with

SRL 6071
(C-3021/2)

8

one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, 5 guanidinyl, OR^9 , NR^9R^{10} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A^-$, $S^+R^9R^{10}A^-$, and $C(O)OM$,

10 wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or R^{13} and R^{14} , together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or 15 more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to which they are attached, form a cyclic ring; and

20 R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^X are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, 25 polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13} , $S^+R^{13}R^{14}A^-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13} , OR^{18} , $S(O)_nNR^{18}$, $NR^{13}R^{18}$, 30 $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid,

SRL 6071
(C-3021/2)

9

peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary

5 heteroaryl can be further substituted with OR^9 , NR^{910} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or $C(O)OM$, and

10 wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

15 wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^{910} , $N^+R^9R^{11}R^{12}A^-$, SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $CONR^9R^{10}$, SO_3R^9 , SO_2OM , $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and $C(O)OM$,

20 wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $N^+R^{13}R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

25 wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;

30 wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,

SRL 6071
(C-3021/2)

10

alkenyl, alkynyl, polyalkyl, polyether, aryl,
haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen,
oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} ,
 $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM ,
5 $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$,
 $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and
 $N^+R^9R^{11}R^{12}A^-$,

provided that both R^5 and R^6 cannot be hydrogen,
OH, or SH and when R^5 is OH, R^1 , R^2 , R^3 , R^4 , R^7 and R^8
10 cannot be all hydrogen;

provided that when R^5 or R^6 is phenyl, only one of
 R^1 or R^2 is H;

provided that when $q = 1$ and R^x is styryl,
anilido, or anilinocarbonyl, only one of R^5 or R^6 is
15 alkyl;

provided that when n is 1, R^1 , R^3 , R^7 , and R^8 are
hydrogen, R^2 is hydrogen, alkyl or aryl, R^4 is
unsubstituted amino or amino substituted with one or
more alkyl or aryl radicals, and R^5 is hydrogen, alkyl
20 or aryl, then R^6 is other than hydroxy; or
a pharmaceutically acceptable salt, solvate, or
prodrug thereof.

Preferably, R^5 and R^6 can independently be
selected from the group consisting of H, aryl,
25 heterocycle, quaternary heterocycle, and quaternary
heteroaryl,

wherein said aryl, heteroaryl, quaternary
heterocycle, and quaternary heteroaryl can be
substituted with one or more substituent groups
30 independently selected from the group consisting of

SRL 6071
(C-3021/2)

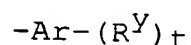
11

alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl,
haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen,
oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} ,
 $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM ,
5 $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$,
 $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{CO}_2\text{R}^{14}$, $\text{OC}(\text{O})\text{R}^{13}$, $\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$,
 $\text{NR}^{13}\text{SOR}^{14}$, $\text{NR}^{13}\text{SO}_2\text{R}^{14}$, $\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$,
 $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and
 $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$,

10 wherein said alkyl, alkenyl, alkynyl, polyalkyl,
polyether, aryl, haloalkyl, cycloalkyl, and heterocycle
can optionally have one or more carbons replaced by O,
 NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 , $\text{P}(\text{O})\text{R}^7$,
 $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene,

15 wherein said alkyl, alkenyl, alkynyl, polyalkyl,
polyether, aryl, haloalkyl, cycloalkyl, and heterocycle
can be further substituted with one or more substituent
groups selected from the group consisting of OR^7 ,
 NR^7R^8 , SR^7 , $\text{S}(\text{O})\text{R}^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo,
20 CONR^7R^8 , $\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$, alkyl, alkenyl, alkynyl, aryl,
cycloalkyl, heterocycle, arylalkyl, quaternary
heterocycle, quaternary heteroaryl, $\text{P}(\text{O})\text{R}^7\text{R}^8$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$,
and $\text{P}(\text{O})(\text{OR}^7)\text{OR}^8$.

25 More preferably, R^5 or R^6 has the formula:



SRL 6071
(C-3021/2)

12

wherein:

t is an integer from 0 to 5;

Ar is selected from the group consisting of
phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl,
5 pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl,
isoquinolinyl, quinoxaliny, imidazolyl, pyrazolyl,
oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl,
triazolyl, isothiazolyl, indolyl, benzoimidazolyl,
benzoxazolyl, benzothiazolyl, and benzoisothiazolyl;
10 and

one or more R^Y are independently selected from the
group consisting of alkyl, alkenyl, alkynyl, polyalkyl,
polyether, aryl, haloalkyl, cycloalkyl, heterocycle,
arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$,
15 SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN ,
 OM , SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} ,
 $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$,
 $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$,
 $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$,
20 $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl,
polyether, aryl, haloalkyl, cycloalkyl, and heterocycle
can be further substituted with one or more substituent
groups selected from the group consisting of OR^7 ,
25 NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN , oxo,
 $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl,
cycloalkyl, heterocycle, arylalkyl, quaternary
heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$,
and $P(O)(OR^7)OR^8$, and

30 wherein said alkyl, alkenyl, alkynyl, polyalkyl,

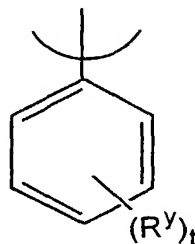
SRL 6071
(C-3021/2)

13

polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}^-$, PR^7 , $\text{P}(\text{O})\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, or phenylene.

5

Most preferably, R^5 or R^6 has the formula (II):



(II)

10

Another embodiment of the invention is further directed to compounds of Formula I wherein at least one or more of the following conditions exist:

(1) R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl. Preferably, R^1 and R^2 are independently selected from the group consisting of C_{1-6} alkyl. More preferably, R^1 and R^2 are the same C_{1-6} alkyl. Still more preferably, R^1 and R^2 are n-butyl; and/or

(2) R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^9 wherein R^9 is defined as set forth above. Preferably, R^3 is hydrogen and R^4 is OR^9 . Still more preferably, R^3 is hydrogen and R^4 is hydroxy; and/or

(3) R^5 is substituted aryl. Preferably, R^5 is substituted phenyl. More preferably, R^5 is phenyl substituted with a radical selected from the group consisting of OR^{13} , $\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$, $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{13}\text{CO}_2\text{R}^{14}$, $\text{OC}(\text{O})\text{R}^{13}$, $\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{SOR}^{14}$, $\text{NR}^{13}\text{SO}_2\text{R}^{14}$, $\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$, and

SRL 6071
(C-3021/2)

14

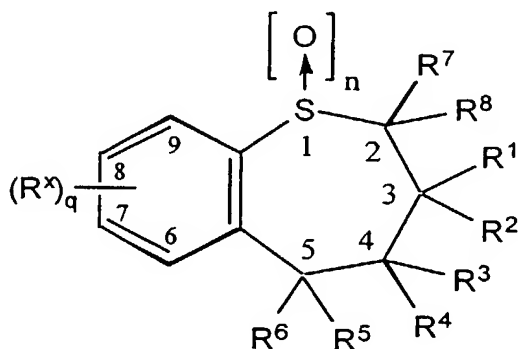
NR¹³SO₂NR¹⁴R¹⁵ wherein R¹³, R¹⁴ and R¹⁵ are as set forth above. Still more preferably, R⁵ is phenyl substituted with OR¹³. Still more preferably, R⁵ is phenyl substituted at the para or meta position with OR¹³ wherein R¹³ comprises a quaternary heterocycle, quaternary heteroaryl or substituted amino; and/or

(4) R⁶ is hydrogen; and/or

(5) R⁷ and R⁸ are independently selected from the group consisting of hydrogen and alkyl. Preferably, R¹ and R² are independently selected from the group C₁₋₆ alkyl. Still more preferably, R¹ and R² are hydrogen; and/or

(6) R^x is selected from the group consisting of OR¹³ and NR¹³R¹⁴. Preferably, R^x is selected from the group consisting of alkoxy, amino, alkylamino and dialkylamino. Still more preferably, R^x is selected from the group consisting of methoxy and dimethylamino.

Another embodiment of the invention is further directed to compounds of formula 1:



(I)

wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R¹ and R² are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

SRL 6071
(C-3021/2)

15

dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

5 wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $N^+R^9R^{10}R^wA^-$, SR^9 , $S^+R^9R^{10}A^-$, $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and

10 $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

15 wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle,

20 carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3 - C_{10} cycloalkyl;

25 R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9 , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 , wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form $=O$, $=NOR^{11}$, $=S$, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

30 wherein R^{11} and R^{12} are independently selected

SRL 6071
(C-3021/2)

16

from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9 , NR^9R^{10} , SR^9 , $S(O)R^9$, SO_2R^9 , SO_3R^9 , CO_2R^9 , CN, halogen, oxo, and $CONR^9R^{10}$,
5 wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2 , and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

10 R^5 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9 , SR^9 , $S(O)R^9$, SO_2R^9 , and SO_3R^9 ,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,
20
25

wherein:

A^- is a pharmaceutically acceptable anion and M is

SRL 6071
(C-3021/2)

17

a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent

5 groups selected from the group consisting of OR^7 ,

NR^7R^8 , SR^7 , $S(O)R^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo,

$CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary

heterocycle, quaternary heteroaryl, $P(O)R^7R^8$,

10 $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O,

NR^7 , $N^+R^7R^8A^-$, S, SO, SO_2 , $S^+R^7A^-$, PR^7 , $P(O)R^7$,

15 $P^+R^7R^8A^-$, or phenylene, and R^{13} , R^{14} , and R^{15} are

independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl,

polyether, aryl, arylalkyl, alkylarylalkyl,

alkylheteroarylalkyl, alkylheterocyclalkyl,

20 cycloalkyl, heterocycle, heteroaryl, quaternary

heterocycle, quaternary heteroaryl, heterocyclalkyl,

heteroarylalkyl, quaternary heterocyclalkyl,

quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

25 wherein alkyl, alkenyl, alkynyl, arylalkyl,

heterocycle, and polyalkyl optionally have one or more

carbons replaced by O, NR^9 , $N^+R^9R^{10}A^-$, S, SO, SO_2 ,

$S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene,

carbohydrate, amino acid, peptide, or polypeptide, and

30 R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting

SRL 6071
(C-3021/2)

18

of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl,
heterocycle, heteroaryl, sulfoalkyl, quaternary
heterocycle, quaternary heteroaryl, quaternary
heterocyclylalkyl, quaternary heteroarylalkyl,
5 guanidiny1, OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$,
 SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM ,
 $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, and
C(O)OM,

wherein R^{16} and R^{17} are independently selected
10 from the substituents constituting R^9 and M; or
 R^{13} and R^{14} , together with the nitrogen atom to
which they are attached form a mono- or polycyclic
heterocycle that is optionally substituted with one or
more radicals selected from the group consisting of
15 oxo, carboxy and quaternary salts; or

R^{14} and R^{15} , together with the nitrogen atom to
which they are attached, form a cyclic ring; and
 R^6 is hydroxy; and

R^7 and R^8 are independently selected from the
20 group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the
group consisting of H, alkyl, alkenyl, alkynyl,
polyalkyl, acyloxy, aryl, arylalkyl, halogen,
haloalkyl, cycloalkyl, heterocycle, heteroaryl,
25 polyether, quaternary heterocycle, quaternary
heteroaryl, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, $\text{S}(\text{O})_2\text{R}^{13}$,
 SO_3R^{13} , $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} ,
CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$,
 $\text{NR}^{14}\text{C}(\text{O})\text{R}^{13}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , OR^{18} , $\text{S}(\text{O})_n\text{NR}^{18}$, $\text{NR}^{13}\text{R}^{18}$,

SRL 6071
(C-3021/2)

19

$\text{NR}^{18}\text{OR}^{14}$, $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, $\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, $\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{C}(\text{O})\text{OM}$, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9 , NR^9R^{10} , $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$, SR^9 , $\text{S}(\text{O})\text{R}^9$, SO_2R^9 , SO_3R^9 , oxo, CO_2R^9 , CN, halogen, $\text{CONR}^9\text{R}^{10}$, SO_3R^9 , SO_2OM , $\text{SO}_2\text{NR}^9\text{R}^{10}$, $\text{PO}(\text{OR}^{16})\text{OR}^{17}$, and $\text{C}(\text{O})\text{OM}$,

wherein in R^x , one or more carbons are optionally replaced by O, NR^{13} , $\text{N}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^{13}\text{A}^-$, PR^{13} , $\text{P}(\text{O})\text{R}^{13}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , $\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$, S, SO, SO_2 , $\text{S}^+\text{R}^9\text{A}^-$, PR^9 , $\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$, or $\text{P}(\text{O})\text{R}^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more

SRL 6071
(C-3021/2)

20

groups selected from the group consisting of alkyl,
alkenyl, alkynyl, polyalkyl, polyether, aryl,
haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen,
oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$, SO_2R^{13} , SO_3R^{13} ,
5 $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN , OM , SO_2OM ,
 $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} , $P(O)R^{13}R^{14}$,
 $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and
 $N^+R^9R^{11}R^{12}A^-$.

provided that both R^5 and R^6 cannot be hydrogen,
10 OH , or SH ;

provided that when R^5 is phenyl, only one of R^1 or
 R^2 is H ; or

a pharmaceutically acceptable salt, solvate, or
prodrug thereof.

15

The invention is further directed to a compound
selected from among:

20 $R^{20} - R^{19} - R^{21}$ (Formula DI)

25
$$\begin{array}{c} R^{22} \\ | \\ R^{20} - R^{19} - R^{21} \end{array}$$
 (Formula DII),

and

30
$$\begin{array}{c} R^{22} \\ | \\ R^{20} - R^{19} - R^{21} \\ | \end{array}$$
 (Formula DIII)

SRL 6071
(C-3021/2)

21

R^{23}

wherein R^{19} is selected from the group
 consisting of alkane diyl, alkene diyl, alkyne diyl,
 5 polyalkane diyl, alkoxy diyl, polyether diyl,
 polyalkoxy diyl, carbohydrate, amino acid, peptide, and
 polypeptide, wherein alkane diyl, alkene diyl, alkyne
 diyl, polyalkane diyl, alkoxy diyl, polyether diyl,
 polyalkoxy diyl, carbohydrate, amino acid, peptide, and
 10 polypeptide can optionally have one or more carbon
 atoms replaced by O, NR^7 , $N^+R^7R^8$, S, SO, SO_2 , $S^+R^7R^8$,
 PR^7 , $P^+R^7R^8$, phenylene, heterocycle, quaternary
 heterocycle, quaternary heteroaryl, or aryl,
 wherein alkane diyl, alkene diyl, alkyne diyl,
 15 polyalkane diyl, alkoxy diyl, polyether diyl,
 polyalkoxy diyl, carbohydrate, amino acid, peptide, and
 polypeptide can be substituted with one or more
 substituent groups independently selected from the
 group consisting of alkyl, alkenyl, alkynyl, polyalkyl,
 20 polyether, aryl, haloalkyl, cycloalkyl, heterocycle,
 arylalkyl, halogen, oxo, OR^{13} , $NR^{13}R^{14}$, SR^{13} , $S(O)R^{13}$,
 SO_2R^{13} , SO_3R^{13} , $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2 , CO_2R^{13} , CN,
 OM, SO_2OM , $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13} ,
 $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and
 25 $N^+R^9R^{11}R^{12}A^-$;

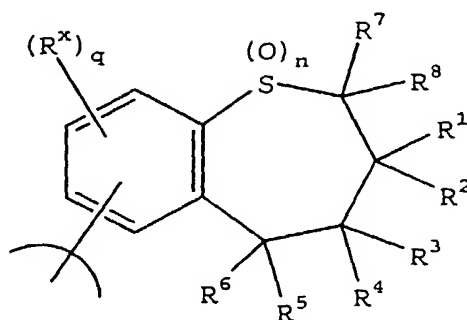
wherein R^{19} further comprises functional linkages
 by which R^{19} is bonded to R^{20} , R^{21} , or R^{22} in the
 compounds of Formulae DII and DIII, and R^{23} in the
 compounds of Formula DIII. Each of R^{20} , R^{21} , or R^{22} and
 30 R^{23} comprises a benzothiepine moiety as described above
 that is therapeutically effective in inhibiting ileal
 bile acid transport.

SRL 6071
(C-3021/2)

22

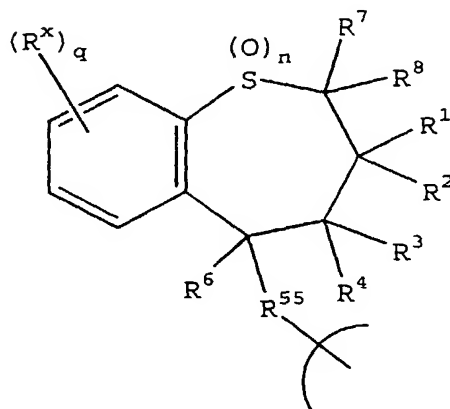
The invention is also directed to a compound selected from among Formula DI, Formula DII and Formula DIII in which each of R^{20} , R^{21} , R^{22} and R^{23} comprises a benzothiepine moiety corresponding to the Formula:

5



(Formula DIV)

or:



(Formula DIVA)

10 wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^x , q , and n are as defined in Formula I as described above, and R^{55} is either a covalent bond or arylene.

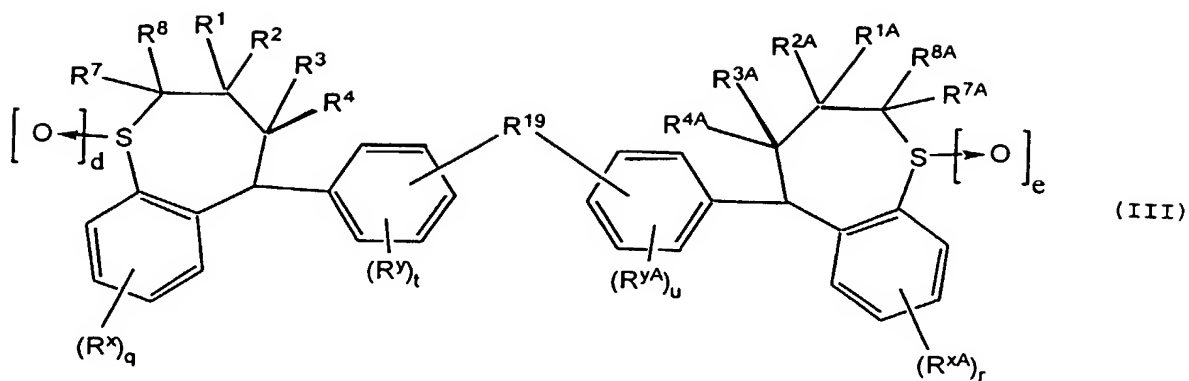
In compounds of Formula DIV, it is particularly preferred that each of R^{20} , R^{21} , and R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII, be bonded at its 7- or 8-position to R^{19} . In compounds of Formula DIVA, it is particularly preferred that R^{55} comprise a phenylene moiety bonded at a *m*- or *p*-carbon thereof to R^{19} .

15

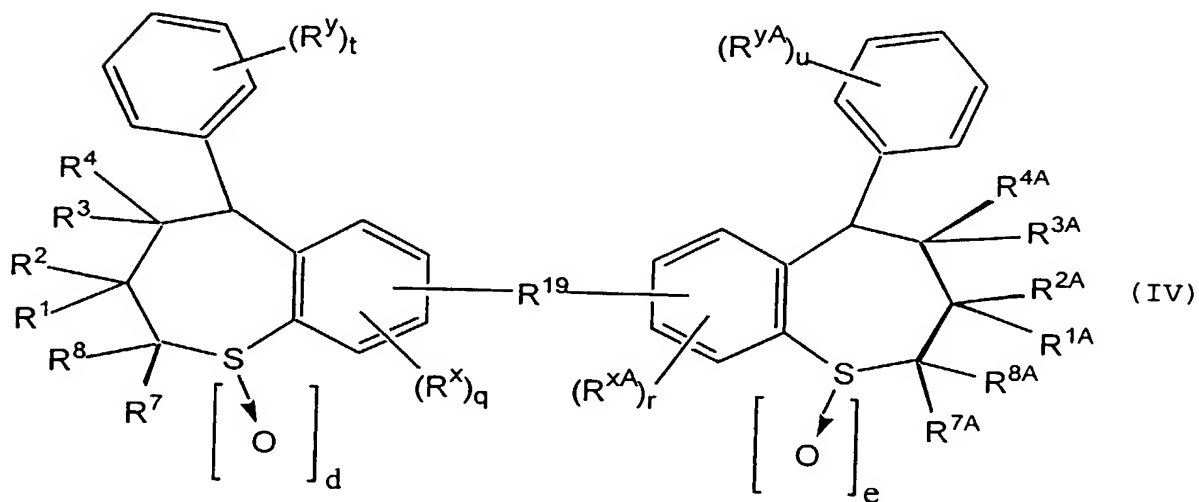
Examples of Formula DI include:

SRL 6071
(C-3021/2)

23



5

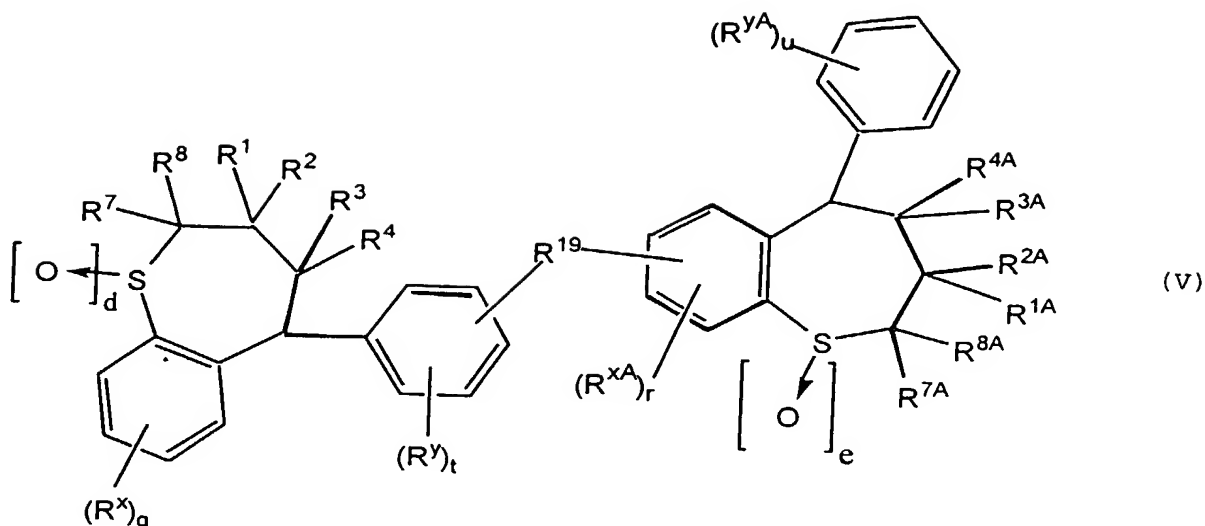


10

and

SRL 6071
(C-3021/2)

24



5 In any of the dimeric or multimeric structures discussed immediately above, benzothiepine compounds of the present invention can be used alone or in various combinations.

10 In any of the compounds of the present invention, R^1 and R^2 can be ethyl/butyl or butyl/butyl.

15 In another aspect, the present invention provides a pharmaceutical composition for the prophylaxis or treatment of a disease or condition for which a bile acid transport inhibitor is indicated, such as a hyperlipidemic condition, for example, atherosclerosis.

20 Such compositions comprise any of the compounds disclosed above, alone or in combination, in an amount effective to reduce bile acid levels in the blood, or to reduce transport thereof across digestive system membranes, and a pharmaceutically acceptable carrier, excipient, or diluent.

In a further aspect, the present invention also provides a method of treating a disease or condition in mammals, including humans, for which a bile acid

SRL 6071
(C-3021/2)

25

transport inhibitor is indicated, comprising administering to a patient in need thereof a compound of the present invention in an effective amount in unit dosage form or in divided doses.

5 In yet a further aspect, the present invention also provides processes for the preparation of compounds of the present invention.

10 Further scope of the applicability of the present invention will become apparent from the detailed description provided below. However, it should be understood that the following detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

20 The following detailed description is provided to aid those skilled in the art in practicing the present invention. Even so, this detailed description should not be construed to unduly limit the present invention as modifications and variations in the embodiments discussed herein can be made by those of ordinary skill in the art without departing from the spirit or scope of the present inventive discovery.

25 The contents of each of the references cited herein, including the contents of the references cited within these primary references, are herein
30 incorporated by reference in their entirety.

Definitions

35 In order to aid the reader in understanding the following detailed description, the following definitions are provided:

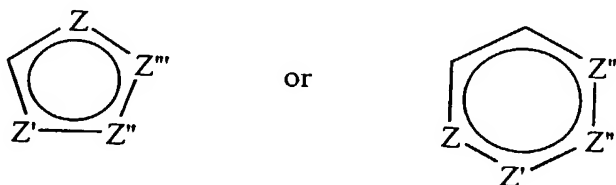
SRL 6071
(C-3021/2)

26

"Alkyl", "alkenyl," and "alkynyl" unless otherwise noted are each straight chain or branched chain hydrocarbons of from one to twenty carbons for alkyl or two to twenty carbons for alkenyl and alkynyl in the present invention and therefore mean, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl and ethenyl, propenyl, butenyl, pentenyl, or hexenyl and ethynyl, propynyl, butynyl, pentynyl, or hexynyl respectively and isomers thereof.

"Aryl" means a fully unsaturated mono- or multi-ring carbocycle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

"Heterocycle" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms can be replaced by N, S, P, or O. This includes, for example, the following structures:



wherein Z, Z', Z'' or Z''' is C, S, P, O, or N, with the proviso that one of Z, Z', Z'' or Z''' is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z', Z'' or Z''' only when each is C.

The term "heteroaryl" means a fully unsaturated heterocycle.

In either "heterocycle" or "heteroaryl," the point of attachment to the molecule of interest can be at the

SRL 6071
(C-3021/2)

27

heteroatom or elsewhere within the ring.

The term "quaternary heterocycle" means a heterocycle in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heterocycle to the molecule of interest can be at a heteroatom or elsewhere.

The term "quaternary heteroaryl" means a heteroaryl in which one or more of the heteroatoms, for example, O, N, S, or P, has such a number of bonds that it is positively charged. The point of attachment of the quaternary heteroaryl to the molecule of interest can be at a heteroatom or elsewhere.

The term "halogen" means a fluoro, chloro, bromo or iodo group.

The term "haloalkyl" means alkyl substituted with one or more halogens.

The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to ten carbon atoms, and wherein any ring can contain one or more double or triple bonds. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepine.

The term "diyl" means a diradical moiety wherein said moiety has two points of attachment to molecules of interest.

The term "oxo" means a doubly bonded oxygen.

The term "polyalkyl" means a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

SRL 6071
(C-3021/2)

28

5 The term "polyether" means a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

 The term "polyalkoxy" means a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, most preferably up to about 5,000.

10 The term "cycloalkylidene" means a mono- or multi-ringed carbocycle wherein a carbon within the ring structure is doubly bonded to an atom which is not within the ring structures.

 The term "carbohydrate" means a mono-, di-, tri-, or polysaccharide wherein the polysaccharide can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan.

15 The term "peptide" means polyamino acid containing up to about 100 amino acid units.

20 The term "polypeptide" means polyamino acid containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid units, most preferably from about 100 amino acid units to about 500 amino acid units.

25 The term "alkylammoniumalkyl" means a NH_2 group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.

30 The term "triazolyl" includes all positional isomers. In all other heterocycles and heteroaryls which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocycles and heteroaryls.

35 The term "sulfo" means a sulfo group, $-\text{SO}_3\text{H}$, or

SRL 6071
(C-3021/2)

29

its salts.

The term "sulfoalkyl" means an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.

5 The term "arylalkyl" means an aryl-substituted alkyl radical such as benzyl. The term "alkylarylalkyl" means an arylalkyl radical that is substituted on the aryl group with one or more alkyl groups.

10 The term "heterocyclylalkyl" means an alkyl radical that is substituted with one or more heterocycle groups. Preferable heterocyclylalkyl radicals are "lower heterocyclylalkyl" radicals having one or more heterocycle groups attached to an alkyl
15 radical having one to ten carbon atoms.

The term "heteroarylalkyl" means an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one or more heteroaryl
20 groups attached to an alkyl radical having one to ten carbon atoms.

The term "quaternary heterocyclylalkyl" means an alkyl radical that is substituted with one or more quaternary heterocycle groups. Preferable quaternary
25 heterocyclylalkyl radicals are "lower quaternary heterocyclylalkyl" radicals having one or more quaternary heterocycle groups attached to an alkyl radical having one to ten carbon atoms.

The term "quaternary heteroarylalkyl" means an
30 alkyl radical that is substituted with one or more quaternary heteroaryl groups. Preferable quaternary heteroarylalkyl radicals are "lower quaternary heteroarylalkyl" radicals having one or more quaternary heteroaryl groups attached to an alkyl radical having
35 one to ten carbon atoms.

SRL 6071
(C-3021/2)

30

5 The term "alkylheteroarylalkyl" means a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are "lower alkylheteroarylalkyl" radicals with alkyl portions having one to ten carbon atoms.

10 The term "alkoxy" an alkyl radical which is attached to the remainder of the molecule by oxygen, such as a methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and tert-butoxy.

15 The term "carboxy" means the carboxy group, $\text{-CO}_2\text{H}$, or its salts.

20 The term "carboxyalkyl" means an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are "lower carboxyalkyl" radicals having one or more carboxy groups attached to an alkyl radical having one to six carbon atoms.

 The term "carboxyheterocycle" means a heterocycle radical that is substituted with one or more carboxy groups.

25 The term "carboxyheteroaryl" means a heteroaryl radical that is substituted with one or more carboxy groups.

30 The term "carboalkoxyalkyl" means an alkyl radical that is substituted with one or more alkoxycarbonyl groups. Preferable carboalkoxyalkyl radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical having one to six carbon atoms.

35 The term "carboxyalkylamino" means an amino radical that is mono- or di-substituted with carboxyalkyl. Preferably, the carboxyalkyl substituent

SRL 6071
(C-3021/2)

31

is a "lower carboxyalkyl" radical wherein the carboxy group is attached to an alkyl radical having one to six carbon atoms.

5 The term "active compound" means a compound of the present invention which inhibits transport of bile acids.

When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.

10 The term "a bile acid transport inhibitor" means a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well as reducing the
15 blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a
20 hyperlipidemic condition such as atherosclerosis.

25 **Compounds**

The compounds of the present invention can have at least two asymmetrical carbon atoms, and therefore include racemates and stereoisomers, such as diastereomers and enantiomers, in both pure form and in
30 admixture. Such stereoisomers can be prepared using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention.

35 Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All

SRL 6071
(C-3021/2)

32

such isomers are contemplated among the compounds of the present invention.

The compounds of the present invention also include tautomers.

5 The compounds of the present invention as discussed below include their salts, solvates and prodrugs.

Compound Syntheses

10 The starting materials for use in the preparation of the compounds of the invention are known or can be prepared by conventional methods known to a skilled person or in an analogous manner to processes described in the art.

15 Generally, the compounds of the present invention can be prepared by the procedures described below.

For example, as shown in Scheme I, reaction of aldehyde II with formaldehyde and sodium hydroxide yields the hydroxyaldehyde III which is converted to mesylate IV with methansulfonyl chloride and
20 triethylamine similar to the procedure described in Chem. Ber. **98**, 728-734 (1965). Reaction of mesylate IV with thiophenol V, prepared by the procedure described in WO 93/16055, in the presence of triethylamine yields
25 keto-aldehyde VI which can be cyclized with the reagent, prepared from zinc and titanium trichloride in refluxing ethylene glycol dimethyl ether (DME), to give a mixture of 2,3-dihydrobenzothiepine VII and two racemic stereoisomers of benzothiepin-(5*H*)-4-one VIII
30 when R¹ and R² are nonequivalent. Oxidation of VII with 3 equivalents of m-chloro-perbenzoic acid (MCPBA) gives isomeric sulfone-epoxides IX which upon hydrogenation with palladium on carbon as the catalyst yield a mixture of four racemic stereoisomers of 4-hydroxy-
35 2,3,4,5-tetrahydrobenzothiepine-1,1-dioxides X and two

SRL 6071
(C-3021/2)

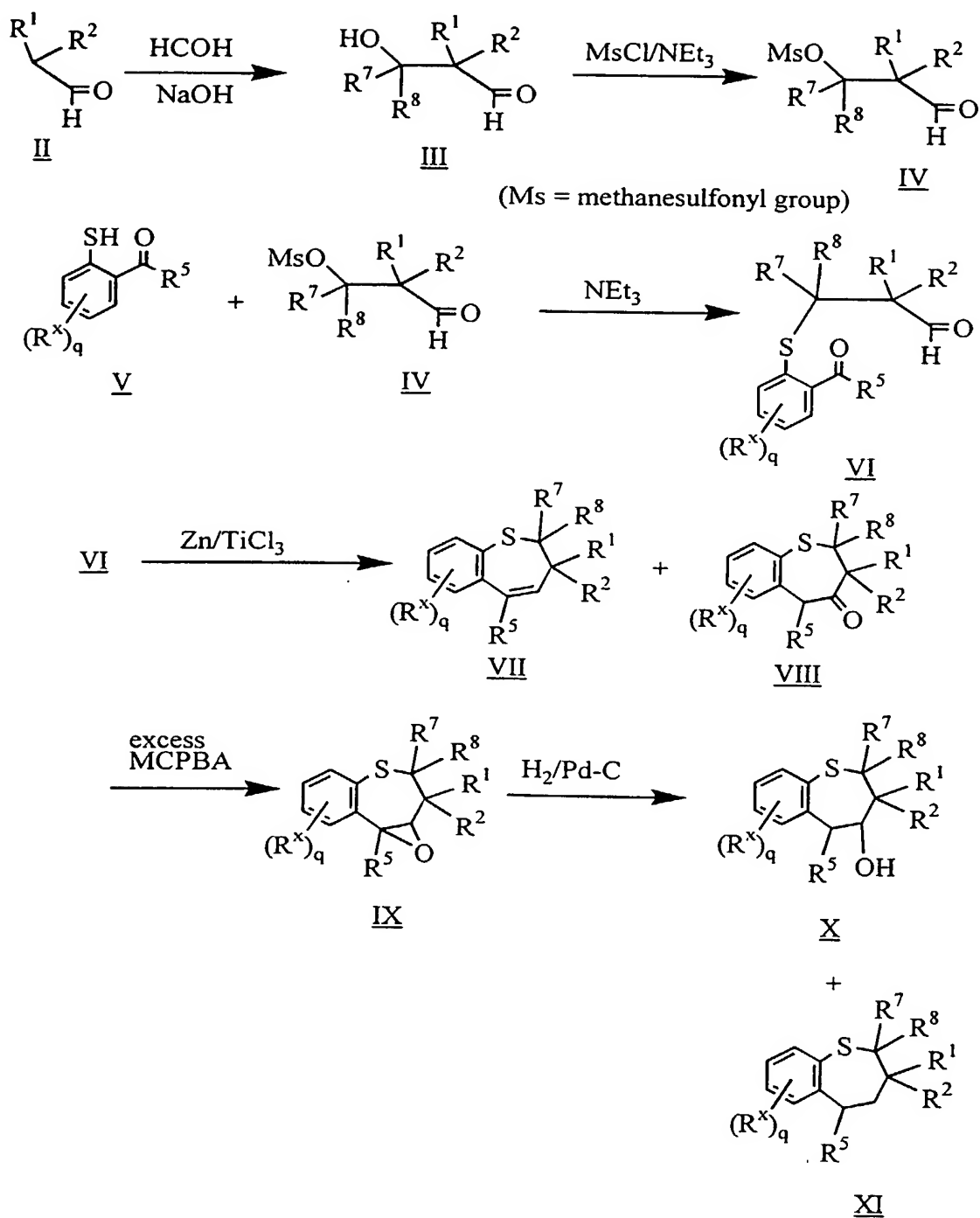
33

racemic stereoisomers of 2,3,4,5-tetrahydro-benzothiepine-1,1-dioxides XI when R^1 and R^2 are nonequivalent.

5 Optically active compounds of the present invention can be prepared by using optically active starting material III or by resolution of compounds X with optical resolution agents well known in the art as described in *J. Org. Chem.*, **39**, 3904 (1974), *ibid.*, **42**, 2781 (1977), and *ibid.*, **44**, 4891 (1979).

SRL 6071
(C-3021/2)

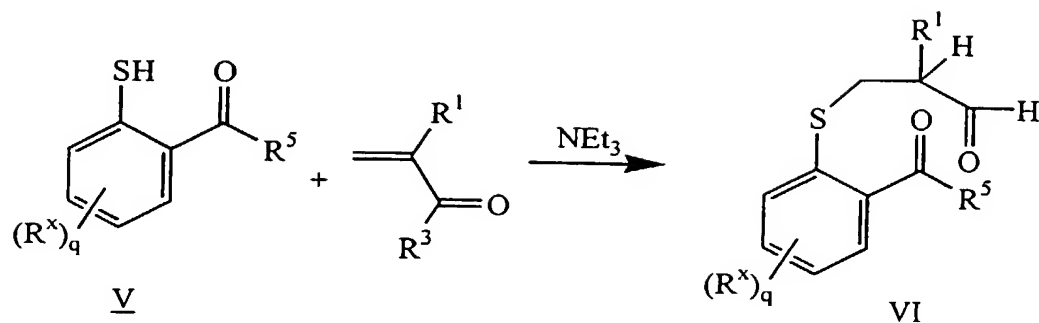
34

Scheme 1

SRL 6071
(C-3021/2)

35

substituted acrolein.



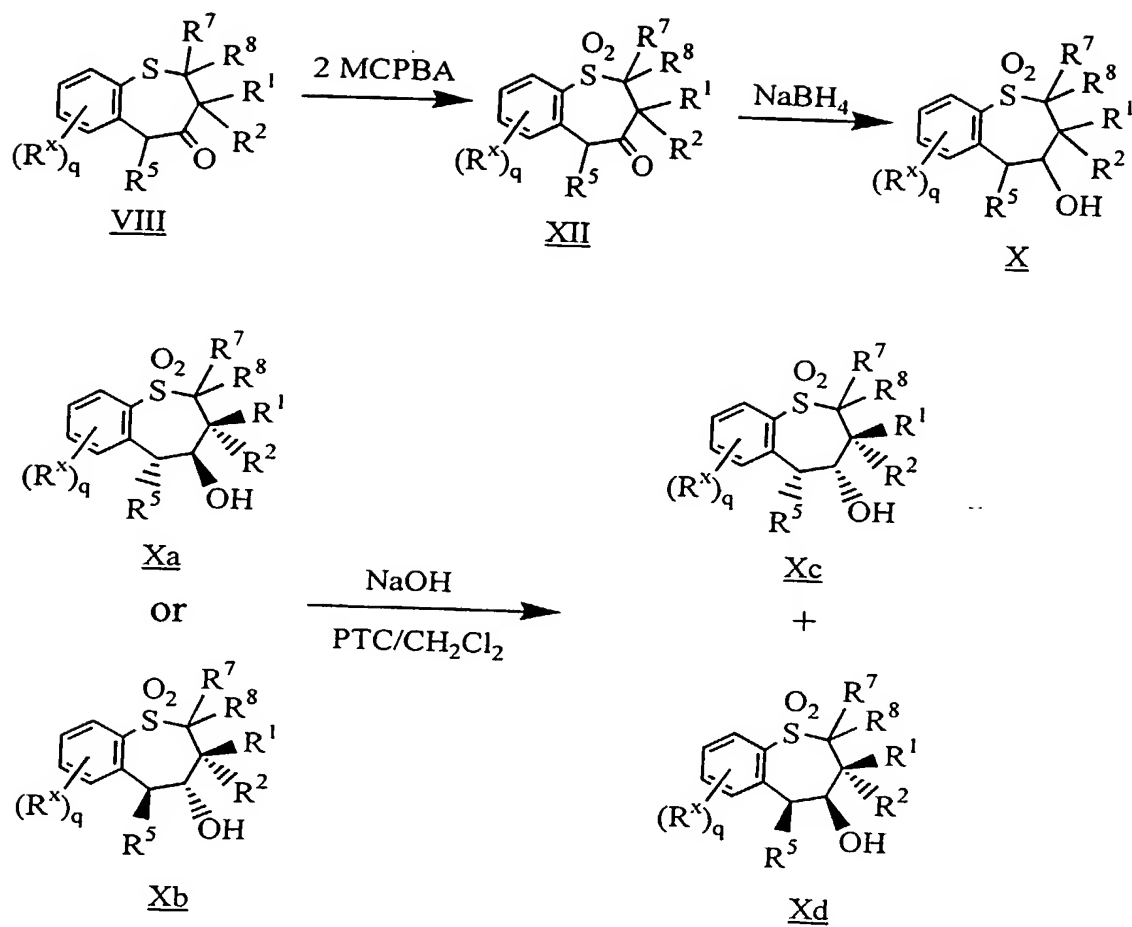
5 Benzothiepin-(5H)-4-one VIII can be oxidized with MCPBA to give the benzothiepin-(5H)-4-one-1,1-dioxide XII which can be reduced with sodium borohydride to give four racemic stereoisomers of X. The two stereoisomers of X, Xa and Xb, having the OH group and R⁵ on the opposite sides of the benzothiepine ring can be

10 converted to the other two isomers of X, Xc and Xd, having the OH group and R⁵ on the same side of the benzothiepine ring by reaction in methylene chloride with 40-50% sodium hydroxide in the presence of a phase transfer catalyst (PTC). The transformation can also

15 be carried out with potassium t-butoxide in THF.

SRL 6071
(C-3021/2)

36



MCPBA = m-chloroperbenzoic acid

PTC = phase transfer catalyst

when R^1 = butyl, R^2 = ethyl, R^5 = phenyl, $X = \text{H}$, $q = 4$

6a = Xa

6b = Xb

6c = Xc

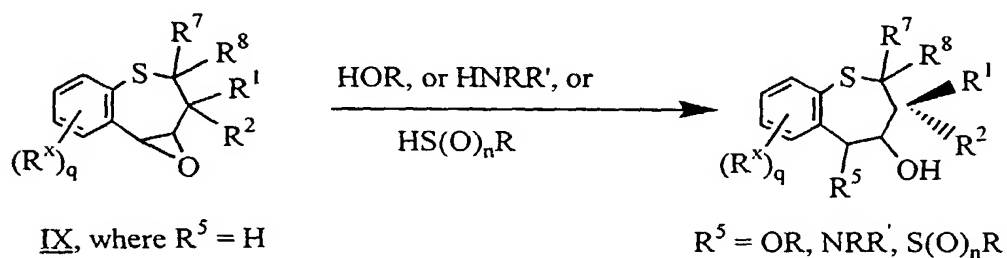
6d = Xd

SRL 6071
(C-3021/2)

37

The compounds of the present invention where R^5 is OR, NRR' and $S(O)_nR$ and R^4 is hydroxy can be prepared by reaction of epoxide IX where R^5 is H with thiol, alcohol, and amine in the presence of a base.

5



Another route to Xc and Xd of the present invention is shown in Scheme 2. Compound VI is oxidized to compound XIII with two equivalent of m-chloroperbenzoic acid. Hydrogenolysis of compound XIII with palladium on carbon yields compound XIV which can be cyclized with either potassium t-butoxide or sodium hydroxide under phase transfer conditions to a mixture of Xc and Xd. Separation of Xc and Xd can be accomplished by either HPLC or fractional crystallization.

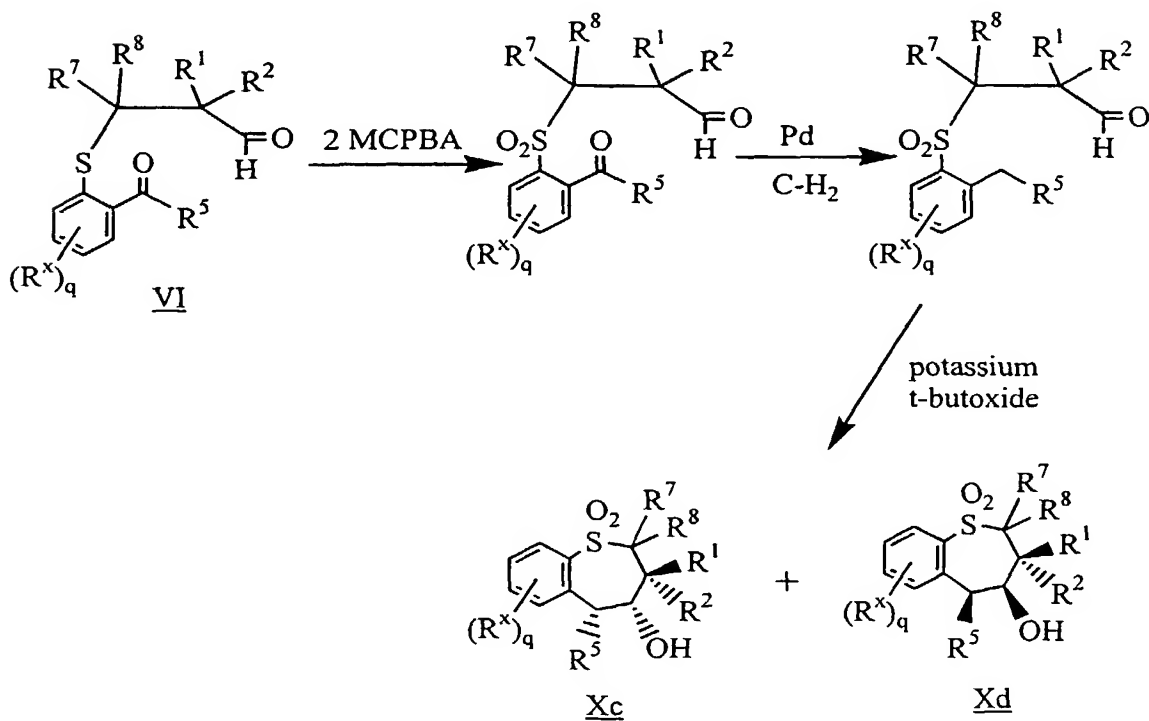
The thiophenols XVIII and V used in the present invention can also be prepared according to the Scheme 3. Alkylation of phenol XV with an arylmethyl chloride in a nonpolar solvent according to the procedure in *J. Chem. Soc.*, 2431-2432 (1958) gives the ortho substituted phenol XVI. The phenol XVI can be converted to the thiophenol XVIII via the thiocarbamate XVII by the procedure described in *J. Org. Chem.*, 31, 3980 (1966). The phenol XVI is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give thiocarbamate XVII which is thermally rearranged

SRL 6071
(C-3021/2)

38

at 200-300 °C, and the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol XVIII. Similarly, Thiophenol V can also be prepared from 2-acylphenol XIX via the intermediate thiocarbamate XX.

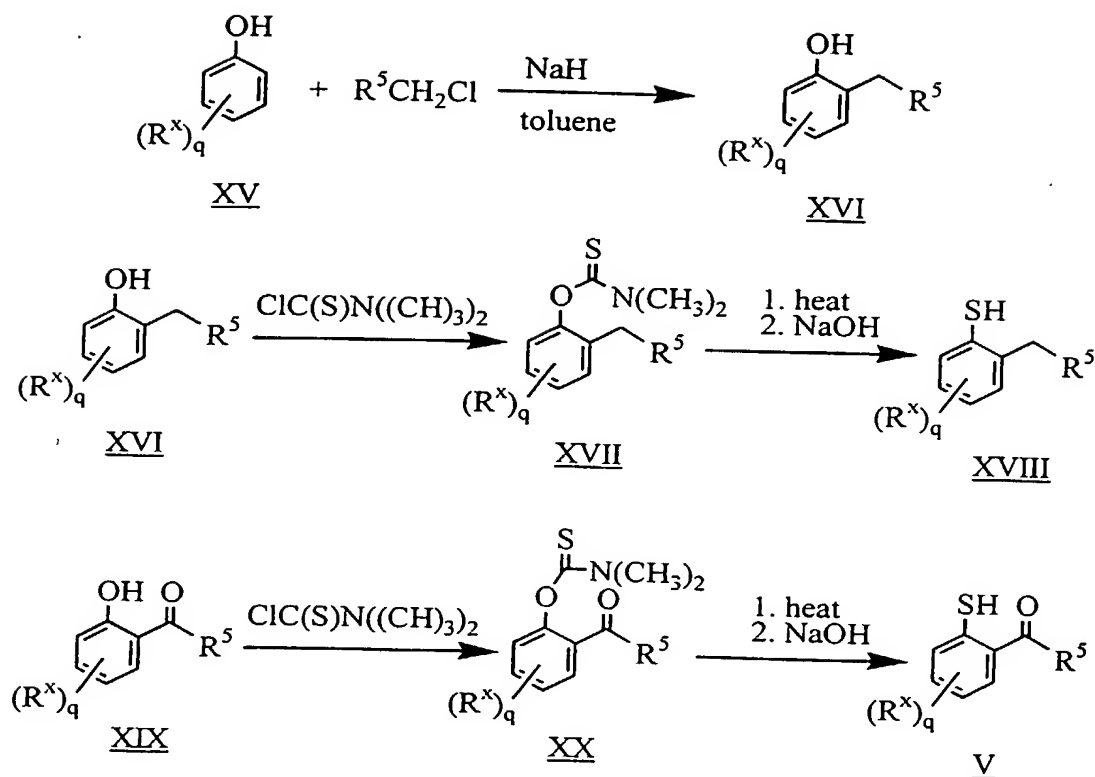
Scheme 2



SRL 6071
(C-3021/2)

39

Scheme 3



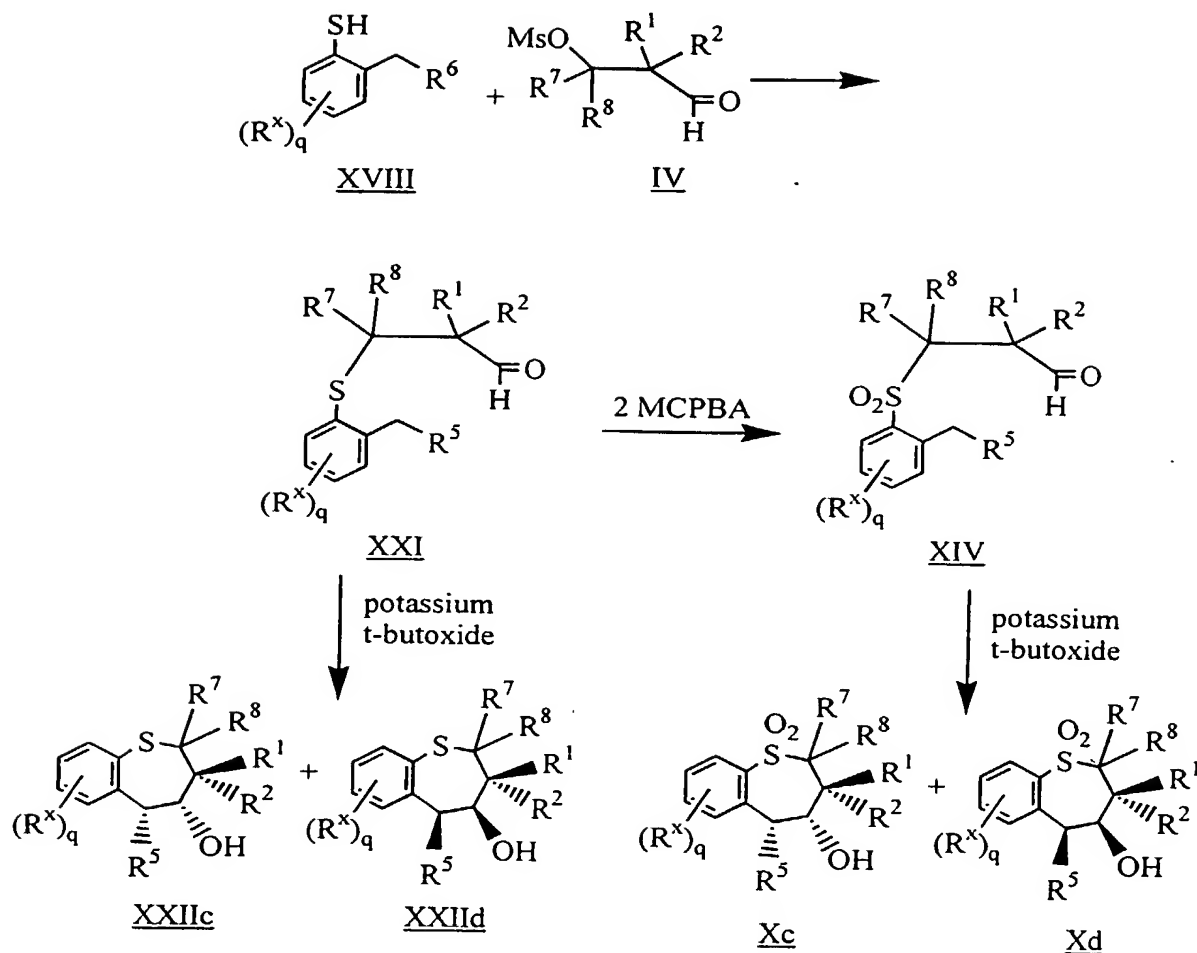
Scheme 4 shows another route to benzothiepine-1,1-dioxides Xc and Xd starting from the thiophenol XVIII.

Compound XVIII can be reacted with mesylate IV to give the sulfide-aldehyde XXI. Oxidation of XXI with two equivalents of MCPBA yields the sulfone-aldehyde XIV which can be cyclized with potassium t-butoxide to a mixture of Xc and Xd. Cyclization of sulfide-aldehyde with potassium t-butoxide also gives a mixture of benzothiepine XXIc and XXIId.

SRL 6071
(C-3021/2)

40

Scheme 4



Examples of amine- and hydroxylamine-containing compounds of the present invention can be prepared as shown in Scheme 5 and Scheme 6. 2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane **32**. Reaction of **32** with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV which can be reduced by hydrogenation to

SRL 6071
(C-3021/2)

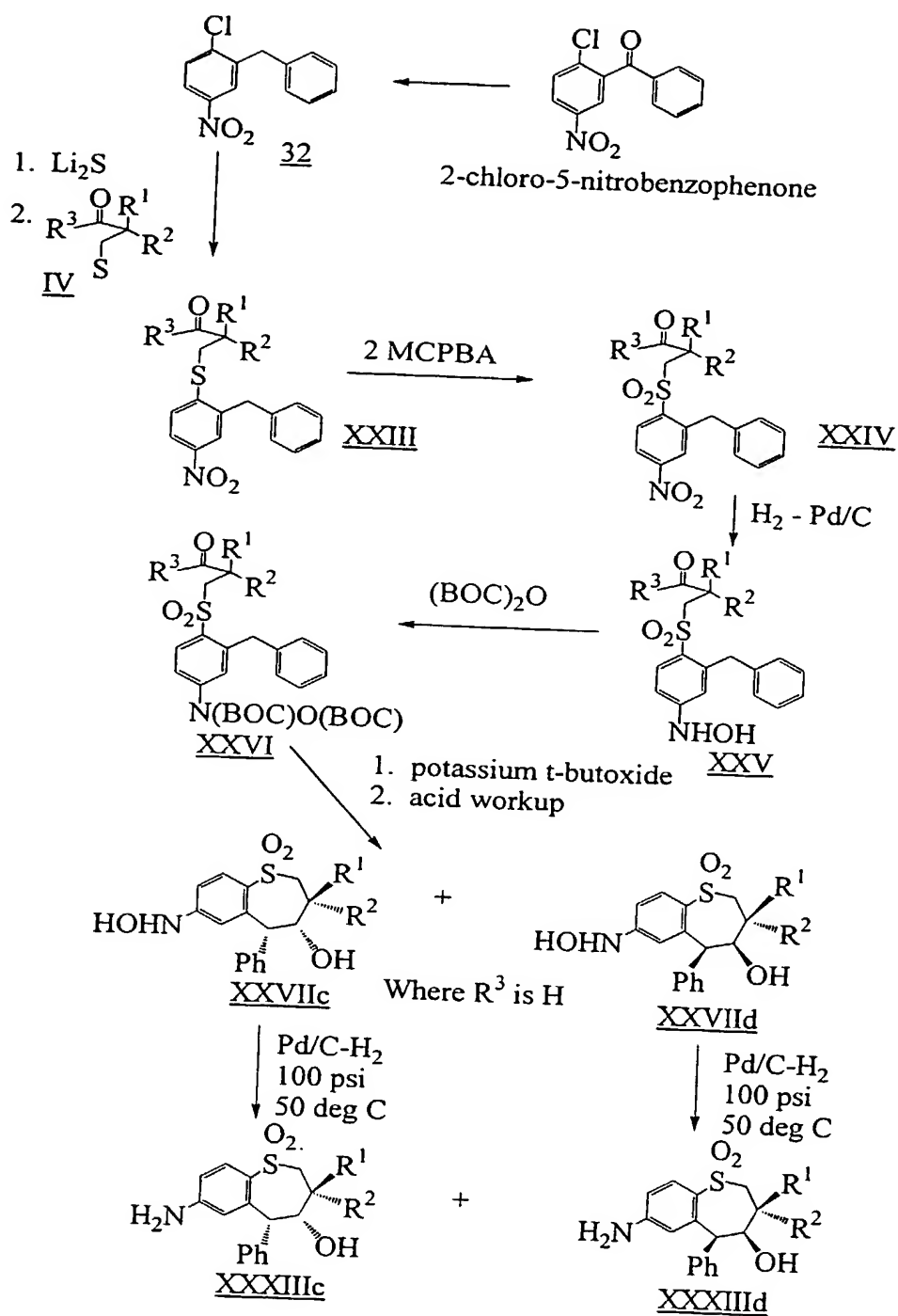
41

5 the hydroxylamine XXV. Protecting the hydroxylamine XXV with di-*t*-butyldicarbonate gives the *N,O*-di-(*t*-butoxycarbonyl)hydroxylamino derivative XXVI. Cyclization of XXVI with potassium *t*-butoxide and removal of the *t*-butoxycarbonyl protecting group gives a mixture of hydroxylamino derivatives XXVIIc and XXVIIId. The primary amine XXXIIIIc and XXXIIIIId derivatives can also be prepared by further hydrogenation of XXIV or XXVIIc and XXVIIId.

SRL 6071
(C-3021/2)

42

Scheme 5



SRL 6071
(C-3021/2)

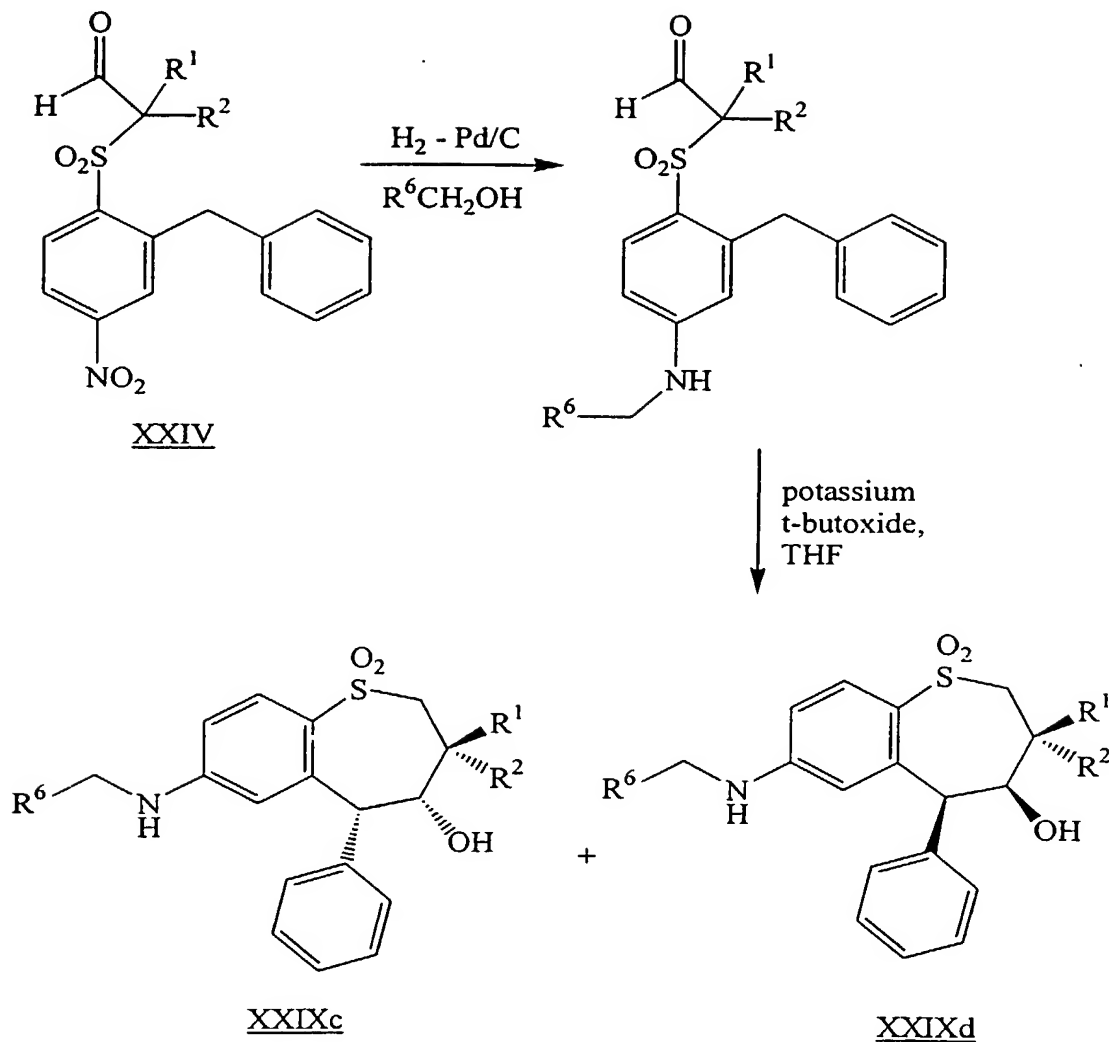
43

5 In Scheme 6, reduction of the sulfone-aldehyde XXV with hydrogen followed by reductive alkylation of the resulting amino derivative with hydrogen and an aldehyde catalyzed by palladium on carbon in the same reaction vessel yields the substituted amine derivative XXVIII. Cyclization of XXVIII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention XXIXc and XXIXd.

SRL 6071
(C-3021/2)

44

Scheme 6

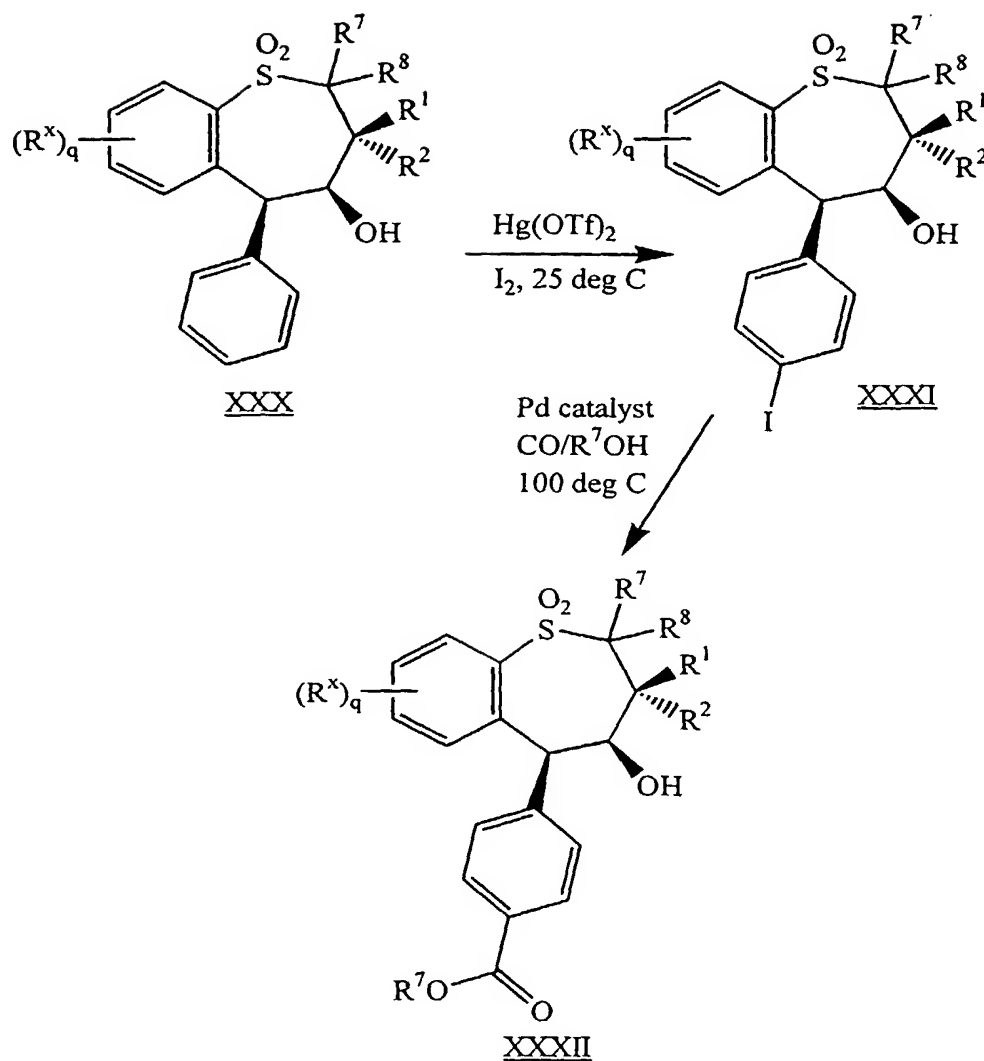


Scheme 7 describes one of the methods of introducing a substituent to the aryl ring at the 5-position of benzothiepine. Iodination of 5-phenyl derivative XXX with iodine catalyzed by mercuric triflate gives the iodo derivative XXXI, which upon palladium-catalyzed carbonylation in an alcohol yields the carboxylate XXXII. Hydrolysis of the carboxylate and derivatization of the resulting acid to acid derivatives are well known in the art.

SRL 6071
(C-3021/2)

45

Scheme 7



Abbreviations used in the foregoing description
have the following meanings:

5

THF---tetrahydrofuran

PTC---phase transfer catalyst

Aliquart 336---methyltricaprylammonium chloride

MCPBA---m-chloroperbenzoic acid

SRL 6071
(C-3021/2)

46

Celite--- a brand of diatomaceous earth filtering
aid
DMF---dimethylformamide
DME---ethylene glycol dimethyl ether
5 BOC---t-butoxycarbonyl group
Me---methyl
Et---ethyl
Bu---butyl
EtOAc---ethyl acetate
10 Et₂O---diethyl ether
CH₂Cl₂---methylene chloride
MgSO₄---magnesium sulfate
NaOH---sodium hydroxide
CH₃OH---methanol
15 HCl---hydrochloric acid
NaCl---sodium chloride
NaH---sodium hydride
LAH---lithium aluminum hydride
LiOH---lithium hydroxide
20 Na₂SO₃---sodium sulfite
NaHCO₃---sodium bicarbonate
DMSO---dimethylsulfoxide
KOSiMe₃---potassium trimethylsilanolate
PEG---polyethylene glycol
25 MS---mass spectrometry
HRMS---high resolution mass spectrometry
ES---electrospray
NMR---nuclear magnetic resonance spectroscopy
GC---gas chromatography
30 MPLC---medium pressure liquid chromatography
HPLC---high pressure liquid chromatography
RPHPLC---reverse phase high pressure liquid
chromatography
RT---room temperature
35 h or hr---hour(s)

SRL 6071
(C-3021/2)

47

min---minute(s)

"Enantiomerically-enriched" (e.e.) means that one enantiomer or set of diastereomers preponderates over the complementary enantiomer or set of diastereomers. Enantiomeric enrichment of a mixture of enantiomers is calculated by dividing the concentration of the preponderating enantiomer by the concentration of the other enantiomer, multiplying the dividend by 100, and expressing the result as a percent. Enantiomeric enrichment can be from about 1% to about 100%, preferably from about 10% to about 100%, and more preferably from about 20% to 100%.

R^1 and R^2 can be selected from among substituted and unsubstituted C_1 to C_{10} alkyl wherein the substituent(s) can be selected from among alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing heterocycles joined to the C_1 to C_{10} alkyl through an ether linkage. Substituents at the 3-carbon can include ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, $-CH_2C(=O)C_2H_5$, $-CH_2OC_2H_5$, and $-CH_2O$ -(4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl are preferred. In certain particularly preferred compounds of the present invention, substituents R^1 and R^2 are identical, for example n-butyl/n-butyl, so that the compound is achiral at the 3-carbon. Eliminating optical isomerism at the 3-carbon simplifies the selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport inhibitor. In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R^*) on the benzo- ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxycarbonylalkyl amine, haloalkylthio, haloalkylsulfinyl,

SRL 6071
(C-3021/2)

48

haloalkylsufonyl, amino, N-alkylamino, N,N-dialkylamino, (N)-alkoxycarbamoyl, (N)-aryloxycarbamoyl, (N)-aralkyloxycarbamoyl, trialkylammonium (especially with a halide counterion),
 5 (N)-amido, (N)-alkylamido, -N-alkylamido, -N,N-dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)-alkylsulfonamido, (N)-haloalkylsulfonamido, carboxyalkyl-amino, trialkylammonium salt, (N)-carbamic acid, alkyl or benzyl ester, N-acylamine,
 10 hydroxylamine, haloacylamine, carbohydrate, thiophene a trialkyl ammonium salt having a carboxylic acid or hydroxy substituent on one or more of the alkyl substituents, an alkylene bridge having a quaternary ammonium salt substituted thereon, $-[O(CH_2)_w]_x-X$ where x is 2 to 12, w is 2 or 3 and X is a halo or a quaternary ammonium salt, and (N)-nitrogen containing heterocycle wherein the nitrogen of said heterocycle is optionally quaternized. Among the preferred species which may constitute R^* are methyl, ethyl, isopropyl, t-butyl,
 15 hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, bromo, fluoro, methylsulfinyl, methylsulfonyl, ethylthio, amino, hydroxylamine, N-methylamino, N,N-dimethylamino, N,N-diethylamino, (N)-benzyloxycarbamoyl, trimethylammonium, A^- ,
 20 $-NHC(=O)CH_3$, $-NHC(=O)C_5H_{11}$, $-NHC(=O)C_6H_{13}$, carboxyethylamino, (N)-morpholinyl, (N)-azetidiny, (N)-N-methylazetidinium A^- , (N)-pyrrolidinyl, pyrrolyl, (N)-N-methylpyridinium A^- , (N)-N-methylmorpholinium A^- , and N-N'-methylpiperazinyl, (N)-bromomethylamido, (N)-
 25 N-hexylamino, thiophene, $-N^+(CH_3)_2CO_2H I^-$, $-NCH_3CH_2CO_2H$, - (N)-N'-dimethylpiperazinium I^- , (N)-t-butylloxycarbamoyl, (N)-methylsulfonamido, (N)N'-methylpyrrolidinium, and $-(OCH_2CH_2)_3I$, where A^- is a pharmaceutically acceptable anion. The benzo ring is
 30 can be mono-substituted at the 6, 7 or 8 position, or
 35

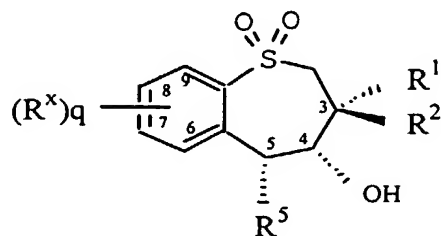
SRL 6071
(C-3021/2)

49

disubstituted at the 7- and -8 positions. Also
included are the 6,7,8-trialkoxy compounds, for example
the 6,7,8-trimethoxy compounds. A variety of other
substituents can be advantageously present on the 6, 7,
5 8, and/or 9- positions of the benzo ring, including,
for example, guanidiny1, cycloalkyl, carbohydrate
(e.g., a 5 or 6 carbon monosaccharide), peptide, and
quaternary ammonium salts linked to the ring via
poly(oxyalkylene) linkages, e.g., $-(OCH_2CH_2)_x-N^+R^{13}R^{14}R^{15}A^-$
10 , where x is 2 to 10. Exemplary compounds are those
set forth below in Table 1.

SRL 6071
(C-3021/2)

50

Table 1: Alternative Compounds #3 (Family F101.xxx.yyy)

| Prefix (FFF.xxx. yyy) | Cpd# yyy) | R ¹ =R ² | R ⁵ | (R ^x) _q |
|-----------------------------|--------------|--------------------------------|----------------|--|
| F101.001 | 01 | ethyl | Ph- | 7-methyl |
| | 02 | ethyl | Ph- | 7-ethyl |
| | 03 | ethyl | Ph- | 7-iso-propyl |
| | 04 | ethyl | Ph- | 7-tert-butyl |
| | 05 | ethyl | Ph- | 7-OH |
| | 06 | ethyl | Ph- | 7-OCH ₃ |
| | 07 | ethyl | Ph- | 7-O(iso-propyl) |
| | 08 | ethyl | Ph- | 7-SCH ₃ |
| | 09 | ethyl | Ph- | 7-SOCH ₃ |
| | 10 | ethyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | ethyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | ethyl | Ph- | 7-NH ₂ |
| | 13 | ethyl | Ph- | 7-NHOH |
| | 14 | ethyl | Ph- | 7-NHCH ₃ |
| | 15 | ethyl | Ph- | 7-N(CH ₃) ₂ |
| | 16 | ethyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | ethyl | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | ethyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | ethyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| | 20 | ethyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | 21 | ethyl | Ph- | 7-(N)-morpholine |
| | 22 | ethyl | Ph- | 7-(N)-azetidine |
| | 23 | ethyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| | 24 | ethyl | Ph- | 7-(N)-pyrrolidine |
| | 25 | ethyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| | 26 | ethyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| | 27 | ethyl | Ph- | 7-(N)-N'-methylpiperazine |
| | 28 | ethyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | 29 | ethyl | Ph- | 7-NH-CBZ |
| | 30 | ethyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| | 31 | ethyl | Ph- | 7-NHC(O)CH ₂ Br |
| | 32 | ethyl | Ph- | 7-NH-C(NH)NH ₂ |

SRL 6071
(C-3021/2)

51

| | | | |
|----|-------|-----|--|
| 33 | ethyl | Ph- | 7-(2)-thiophene |
| 34 | ethyl | Ph- | 8-methyl |
| 35 | ethyl | Ph- | 8-ethyl |
| 36 | ethyl | Ph- | 8-iso-propyl |
| 37 | ethyl | Ph- | 8-tert-butyl |
| 38 | ethyl | Ph- | 8-OH |
| 39 | ethyl | Ph- | 8-OCH ₃ |
| 40 | ethyl | Ph- | 8-O(iso-propyl) |
| 41 | ethyl | Ph- | 8-SCH ₃ |
| 42 | ethyl | Ph- | 8-SOCH ₃ |
| 43 | ethyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | ethyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | ethyl | Ph- | 8-NH ₂ |
| 46 | ethyl | Ph- | 8-NHOH |
| 47 | ethyl | Ph- | 8-NHCH ₃ |
| 48 | ethyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | ethyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | ethyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | ethyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | ethyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | ethyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | ethyl | Ph- | 8-(N)-morpholine |
| 55 | ethyl | Ph- | 8-(N)-azetidine |
| 56 | ethyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | ethyl | Ph- | 8-(N)-pyrrolidine |
| 58 | ethyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | ethyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | ethyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | ethyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | ethyl | Ph- | 8-NH-CBZ |
| 63 | ethyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | ethyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | ethyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | ethyl | Ph- | 8-(2)-thiophene |
| 67 | ethyl | Ph- | 9-methyl |
| 68 | ethyl | Ph- | 9-ethyl |
| 69 | ethyl | Ph- | 9-iso-propyl |
| 70 | ethyl | Ph- | 9-tert-butyl |
| 71 | ethyl | Ph- | 9-OH |
| 72 | ethyl | Ph- | 9-OCH ₃ |
| 73 | ethyl | Ph- | 9-O(iso-propyl) |
| 74 | ethyl | Ph- | 9-SCH ₃ |

SRL 6071
(C-3021/2)

52

| | | | |
|-----|-------|-----|--|
| 75 | ethyl | Ph- | 9-SOCH ₃ |
| 76 | ethyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | ethyl | Ph- | 9-SCH ₂ CH ₃ |
| 78 | ethyl | Ph- | 9-NH ₂ |
| 79 | ethyl | Ph- | 9-NHOH |
| 80 | ethyl | Ph- | 9-NHCH ₃ |
| 81 | ethyl | Ph- | 9-N(CH ₃) ₂ |
| 82 | ethyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | ethyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | ethyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | ethyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | ethyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | ethyl | Ph- | 9-(N)-morpholine |
| 88 | ethyl | Ph- | 9-(N)-azetidine |
| 89 | ethyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | ethyl | Ph- | 9-(N)-pyrrolidine |
| 91 | ethyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | ethyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | ethyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | ethyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | ethyl | Ph- | 9-NH-CBZ |
| 96 | ethyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | ethyl | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | ethyl | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | ethyl | Ph- | 9-(2)-thiophene |
| 100 | ethyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | ethyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | ethyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | ethyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |

| | | | | |
|----------|----|----------|-----|------------------------------------|
| F101.002 | 01 | n-propyl | Ph- | 7-methyl |
| | 02 | n-propyl | Ph- | 7-ethyl |
| | 03 | n-propyl | Ph- | 7-iso-propyl |
| | 04 | n-propyl | Ph- | 7-tert-butyl |
| | 05 | n-propyl | Ph- | 7-OH |
| | 06 | n-propyl | Ph- | 7-OCH ₃ |
| | 07 | n-propyl | Ph- | 7-O(iso-propyl) |
| | 08 | n-propyl | Ph- | 7-SCH ₃ |
| | 09 | n-propyl | Ph- | 7-SOCH ₃ |
| | 10 | n-propyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | n-propyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | n-propyl | Ph- | 7-NH ₂ |

SRL 6071
(C-3021/2)

53

| | | | |
|----|----------|-----|--|
| 13 | n-propyl | Ph- | 7-NHOH |
| 14 | n-propyl | Ph- | 7-NHCH ₃ |
| 15 | n-propyl | Ph- | 7-N(CH ₃) ₂ |
| 16 | n-propyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| 17 | n-propyl | Ph- | 7-NHC(=O)CH ₃ |
| 18 | n-propyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| 19 | n-propyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| 20 | n-propyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 21 | n-propyl | Ph- | 7-(N)-morpholine |
| 22 | n-propyl | Ph- | 7-(N)-azetidine |
| 23 | n-propyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| 24 | n-propyl | Ph- | 7-(N)-pyrrolidine |
| 25 | n-propyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 26 | n-propyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| 27 | n-propyl | Ph- | 7-(N)-N'-methylpiperazine |
| 28 | n-propyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| 29 | n-propyl | Ph- | 7-NH-CBZ |
| 30 | n-propyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| 31 | n-propyl | Ph- | 7-NHC(O)CH ₂ Br |
| 32 | n-propyl | Ph- | 7-NH-C(NH)NH ₂ |
| 33 | n-propyl | Ph- | 7-(2)-thiophene |
| 34 | n-propyl | Ph- | 8-methyl |
| 35 | n-propyl | Ph- | 8-ethyl |
| 36 | n-propyl | Ph- | 8-iso-propyl |
| 37 | n-propyl | Ph- | 8-tert-butyl |
| 38 | n-propyl | Ph- | 8-OH |
| 39 | n-propyl | Ph- | 8-OCH ₃ |
| 40 | n-propyl | Ph- | 8-O(iso-propyl) |
| 41 | n-propyl | Ph- | 8-SCH ₃ |
| 42 | n-propyl | Ph- | 8-SOCH ₃ |
| 43 | n-propyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | n-propyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | n-propyl | Ph- | 8-NH ₂ |
| 46 | n-propyl | Ph- | 8-NHOH |
| 47 | n-propyl | Ph- | 8-NHCH ₃ |
| 48 | n-propyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | n-propyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | n-propyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | n-propyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | n-propyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | n-propyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | n-propyl | Ph- | 8-(N)-morpholine |

SRL 6071
(C-3021/2)

54

| | | | |
|----|----------|-----|--|
| 55 | n-propyl | Ph- | 8-(N)-azetidine |
| 56 | n-propyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | n-propyl | Ph- | 8-(N)-pyrrolidine |
| 58 | n-propyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | n-propyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | n-propyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | n-propyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | n-propyl | Ph- | 8-NH-CBZ |
| 63 | n-propyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | n-propyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | n-propyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | n-propyl | Ph- | 8-(2)-thiophene |
| 67 | n-propyl | Ph- | 9-methyl |
| 68 | n-propyl | Ph- | 9-ethyl |
| 69 | n-propyl | Ph- | 9-iso-propyl |
| 70 | n-propyl | Ph- | 9-tert-butyl |
| 71 | n-propyl | Ph- | 9-OH |
| 72 | n-propyl | Ph- | 9-OCH ₃ |
| 73 | n-propyl | Ph- | 9-O(iso-propyl) |
| 74 | n-propyl | Ph- | 9-SCH ₃ |
| 75 | n-propyl | Ph- | 9-SOCH ₃ |
| 76 | n-propyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | n-propyl | Ph- | 9-SCH ₂ CH ₃ |
| 78 | n-propyl | Ph- | 9-NH ₂ |
| 79 | n-propyl | Ph- | 9-NHOH |
| 80 | n-propyl | Ph- | 9-NHCH ₃ |
| 81 | n-propyl | Ph- | 9-N(CH ₃) ₂ |
| 82 | n-propyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | n-propyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | n-propyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | n-propyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | n-propyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | n-propyl | Ph- | 9-(N)-morpholine |
| 88 | n-propyl | Ph- | 9-(N)-azetidine |
| 89 | n-propyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | n-propyl | Ph- | 9-(N)-pyrrolidine |
| 91 | n-propyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | n-propyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | n-propyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | n-propyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | n-propyl | Ph- | 9-NH-CBZ |
| 96 | n-propyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |

SRL 6071
(C-3021/2)

55

| | | | | |
|----------|-----|----------|-----|--|
| | 97 | n-propyl | Ph- | 9-NHC(O)CH ₂ Br |
| | 98 | n-propyl | Ph- | 9-NH-C(NH)NH ₂ |
| | 99 | n-propyl | Ph- | 9-(2)-thiophene |
| | 100 | n-propyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| | 101 | n-propyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| | 102 | n-propyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| | 103 | n-propyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |
| <hr/> | | | | |
| F101.003 | 01 | n-butyl | Ph- | 7-methyl |
| | 02 | n-butyl | Ph- | 7-ethyl |
| | 03 | n-butyl | Ph- | 7-iso-propyl |
| | 04 | n-butyl | Ph- | 7-tert-butyl |
| | 05 | n-butyl | Ph- | 7-OH |
| | 06 | n-butyl | Ph- | 7-OCH ₃ |
| | 07 | n-butyl | Ph- | 7-O(iso-propyl) |
| | 08 | n-butyl | Ph- | 7-SCH ₃ |
| | 09 | n-butyl | Ph- | 7-SOCH ₃ |
| | 10 | n-butyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | n-butyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | n-butyl | Ph- | 7-NH ₂ |
| | 13 | n-butyl | Ph- | 7-NHOH |
| | 14 | n-butyl | Ph- | 7-NHCH ₃ |
| | 15 | n-butyl | Ph- | 7-N(CH ₃) ₂ |
| | 16 | n-butyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | n-butyl | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | n-butyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | n-butyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| | 20 | n-butyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | 21 | n-butyl | Ph- | 7-(N)-morpholine |
| | 22 | n-butyl | Ph- | 7-(N)-azetidine |
| | 23 | n-butyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| | 24 | n-butyl | Ph- | 7-(N)-pyrrolidine |
| | 25 | n-butyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| | 26 | n-butyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| | 27 | n-butyl | Ph- | 7-(N)-N'-methylpiperazine |
| | 28 | n-butyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | 29 | n-butyl | Ph- | 7-NH-CBZ |
| | 30 | n-butyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| | 31 | n-butyl | Ph- | 7-NHC(O)CH ₂ Br |
| | 32 | n-butyl | Ph- | 7-NH-C(NH)NH ₂ |
| | 33 | n-butyl | Ph- | 7-(2)-thiophene |
| | 34 | n-butyl | Ph- | 8-methyl |

SRL 6071
(C-3021/2)

56

| | | | |
|----|---------|-----|--|
| 35 | n-butyl | Ph- | 8-ethyl |
| 36 | n-butyl | Ph- | 8-iso-propyl |
| 37 | n-butyl | Ph- | 8-tert-butyl |
| 38 | n-butyl | Ph- | 8-OH |
| 39 | n-butyl | Ph- | 8-OCH ₃ |
| 40 | n-butyl | Ph- | 8-O(iso-propyl) |
| 41 | n-butyl | Ph- | 8-SCH ₃ |
| 42 | n-butyl | Ph- | 8-SOCH ₃ |
| 43 | n-butyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | n-butyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | n-butyl | Ph- | 8-NH ₂ |
| 46 | n-butyl | Ph- | 8-NHOH |
| 47 | n-butyl | Ph- | 8-NHCH ₃ |
| 48 | n-butyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | n-butyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | n-butyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | n-butyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | n-butyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | n-butyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | n-butyl | Ph- | 8-(N)-morpholine |
| 55 | n-butyl | Ph- | 8-(N)-azetidine |
| 56 | n-butyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | n-butyl | Ph- | 8-(N)-pyrrolidine |
| 58 | n-butyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | n-butyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | n-butyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | n-butyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | n-butyl | Ph- | 8-NH-CBZ |
| 63 | n-butyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | n-butyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | n-butyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | n-butyl | Ph- | 8-(2)-thiophene |
| 67 | n-butyl | Ph- | 9-methyl |
| 68 | n-butyl | Ph- | 9-ethyl |
| 69 | n-butyl | Ph- | 9-iso-propyl |
| 70 | n-butyl | Ph- | 9-tert-butyl |
| 71 | n-butyl | Ph- | 9-OH |
| 72 | n-butyl | Ph- | 9-OCH ₃ |
| 73 | n-butyl | Ph- | 9-O(iso-propyl) |
| 74 | n-butyl | Ph- | 9-SCH ₃ |
| 75 | n-butyl | Ph- | 9-SOCH ₃ |
| 76 | n-butyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | n-butyl | Ph- | 9-SCH ₂ CH ₃ |

SRL 6071
(C-3021/2)

57

| | | | |
|-----|---------|-----|--|
| 78 | n-butyl | Ph- | 9-NH ₂ |
| 79 | n-butyl | Ph- | 9-NHOH |
| 80 | n-butyl | Ph- | 9-NHCH ₃ |
| 81 | n-butyl | Ph- | 9-N(CH ₃) ₂ |
| 82 | n-butyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | n-butyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | n-butyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | n-butyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | n-butyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | n-butyl | Ph- | 9-(N)-morpholine |
| 88 | n-butyl | Ph- | 9-(N)-azetidine |
| 89 | n-butyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | n-butyl | Ph- | 9-(N)-pyrrolidine |
| 91 | n-butyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | n-butyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | n-butyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | n-butyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | n-butyl | Ph- | 9-NH-CBZ |
| 96 | n-butyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | n-butyl | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | n-butyl | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | n-butyl | Ph- | 9-(2)-thiophene |
| 100 | n-butyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | n-butyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | n-butyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | n-butyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |

| | | | | |
|----------|----|----------|-----|------------------------------------|
| F101.004 | 01 | n-pentyl | Ph- | 7-methyl |
| | 02 | n-pentyl | Ph- | 7-ethyl |
| | 03 | n-pentyl | Ph- | 7-iso-propyl |
| | 04 | n-pentyl | Ph- | 7-tert-butyl |
| | 05 | n-pentyl | Ph- | 7-OH |
| | 06 | n-pentyl | Ph- | 7-OCH ₃ |
| | 07 | n-pentyl | Ph- | 7-O(iso-propyl) |
| | 08 | n-pentyl | Ph- | 7-SCH ₃ |
| | 09 | n-pentyl | Ph- | 7-SOCH ₃ |
| | 10 | n-pentyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | n-pentyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | n-pentyl | Ph- | 7-NH ₂ |
| | 13 | n-pentyl | Ph- | 7-NHOH |
| | 14 | n-pentyl | Ph- | 7-NHCH ₃ |
| | 15 | n-pentyl | Ph- | 7-N(CH ₃) ₂ |

SRL 6071
(C-3021/2)

58

| | | | |
|----|----------|-----|--|
| 16 | n-pentyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| 17 | n-pentyl | Ph- | 7-NHC(=O)CH ₃ |
| 18 | n-pentyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| 19 | n-pentyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| 20 | n-pentyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 21 | n-pentyl | Ph- | 7-(N)-morpholine |
| 22 | n-pentyl | Ph- | 7-(N)-azetidine |
| 23 | n-pentyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| 24 | n-pentyl | Ph- | 7-(N)-pyrrolidine |
| 25 | n-pentyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 26 | n-pentyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| 27 | n-pentyl | Ph- | 7-(N)-N'-methylpiperazine |
| 28 | n-pentyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| 29 | n-pentyl | Ph- | 7-NH-CBZ |
| 30 | n-pentyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| 31 | n-pentyl | Ph- | 7-NHC(O)CH ₂ Br |
| 32 | n-pentyl | Ph- | 7-NH-C(NH)NH ₂ |
| 33 | n-pentyl | Ph- | 7-(2)-thiophene |
| 34 | n-pentyl | Ph- | 8-methyl |
| 35 | n-pentyl | Ph- | 8-ethyl |
| 36 | n-pentyl | Ph- | 8-iso-propyl |
| 37 | n-pentyl | Ph- | 8-tert-butyl |
| 38 | n-pentyl | Ph- | 8-OH |
| 39 | n-pentyl | Ph- | 8-OCH ₃ |
| 40 | n-pentyl | Ph- | 8-O(iso-propyl) |
| 41 | n-pentyl | Ph- | 8-SCH ₃ |
| 42 | n-pentyl | Ph- | 8-SOCH ₃ |
| 43 | n-pentyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | n-pentyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | n-pentyl | Ph- | 8-NH ₂ |
| 46 | n-pentyl | Ph- | 8-NHOH |
| 47 | n-pentyl | Ph- | 8-NHCH ₃ |
| 48 | n-pentyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | n-pentyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | n-pentyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | n-pentyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | n-pentyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | n-pentyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | n-pentyl | Ph- | 8-(N)-morpholine |
| 55 | n-pentyl | Ph- | 8-(N)-azetidine |
| 56 | n-pentyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | n-pentyl | Ph- | 8-(N)-pyrrolidine |

SRL 6071
(C-3021/2)

59

58 n-pentyl
59 n-pentyl
60 n-pentyl
61 n-pentyl
62 n-pentyl
63 n-pentyl
64 n-pentyl
65 n-pentyl
66 n-pentyl

67 n-pentyl
68 n-pentyl
69 n-pentyl
70 n-pentyl
71 n-pentyl
72 n-pentyl
73 n-pentyl
74 n-pentyl
75 n-pentyl
76 n-pentyl
77 n-pentyl
78 n-pentyl
79 n-pentyl
80 n-pentyl
81 n-pentyl
82 n-pentyl
83 n-pentyl
84 n-pentyl
85 n-pentyl
86 n-pentyl
87 n-pentyl
88 n-pentyl
89 n-pentyl
90 n-pentyl
91 n-pentyl
92 n-pentyl
93 n-pentyl
93 n-pentyl
95 n-pentyl
96 n-pentyl
97 n-pentyl
98 n-pentyl
99 n-pentyl

Ph- 8-(N)-N-methyl-pyrrolidinium, I⁻
Ph- 8-(N)-N-methyl-morpholinium, I⁻
Ph- 8-(N)-N'-methylpiperazine
Ph- 8-(N)-N'-dimethylpiperazinium, I⁻
Ph- 8-NH-CBZ
Ph- 8-NHC(O)C₅H₁₁
Ph- 8-NHC(O)CH₂Br
Ph- 8-NH-C(NH)NH₂
Ph- 8-(2)-thiophene

Ph- 9-methyl
Ph- 9-ethyl
Ph- 9-iso-propyl
Ph- 9-tert-butyl
Ph- 9-OH
Ph- 9-OCH₃
Ph- 9-O(iso-propyl)
Ph- 9-SCH₃
Ph- 9-SOCH₃
Ph- 9-SO₂CH₃
Ph- 9-SCH₂CH₃
Ph- 9-NH₂
Ph- 9-NHOH
Ph- 9-NHCH₃
Ph- 9-N(CH₃)₂
Ph- 9-N⁺(CH₃)₃, I⁻
Ph- 9-NHC(=O)CH₃
Ph- 9-N(CH₂CH₃)₂
Ph- 9-NMeCH₂CO₂H
Ph- 9-N⁺(Me)₂CH₂CO₂H, I⁻
Ph- 9-(N)-morpholine
Ph- 9-(N)-azetidine
Ph- 9-(N)-N-methylazetidinium, I⁻
Ph- 9-(N)-pyrrolidine
Ph- 9-(N)-N-methyl-pyrrolidinium, I⁻
Ph- 9-(N)-N-methyl-morpholinium, I⁻
Ph- 9-(N)-N'-methylpiperazine
Ph- 9-(N)-N'-dimethylpiperazinium, I⁻
Ph- 9-NH-CBZ
Ph- 9-NHC(O)C₅H₁₁
Ph- 9-NHC(O)CH₂Br
Ph- 9-NH-C(NH)NH₂
Ph- 9-(2)-thiophene

SRL 6071
(C-3021/2)

60

| | | | | |
|----------|-----|----------|-----|--|
| | 100 | n-pentyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| | 101 | n-pentyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| | 102 | n-pentyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| | 103 | n-pentyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |
| <hr/> | | | | |
| F101.005 | 01 | n-hexyl | Ph- | 7-methyl |
| | 02 | n-hexyl | Ph- | 7-ethyl |
| | 03 | n-hexyl | Ph- | 7-iso-propyl |
| | 04 | n-hexyl | Ph- | 7-tert-butyl |
| | 05 | n-hexyl | Ph- | 7-OH |
| | 06 | n-hexyl | Ph- | 7-OCH ₃ |
| | 07 | n-hexyl | Ph- | 7-O(iso-propyl) |
| | 08 | n-hexyl | Ph- | 7-SCH ₃ |
| | 09 | n-hexyl | Ph- | 7-SOCH ₃ |
| | 10 | n-hexyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | n-hexyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | n-hexyl | Ph- | 7-NH ₂ |
| | 13 | n-hexyl | Ph- | 7-NHOH |
| | 14 | n-hexyl | Ph- | 7-NHCH ₃ |
| | 15 | n-hexyl | Ph- | 7-N(CH ₃) ₂ |
| | 16 | n-hexyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | n-hexyl | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | n-hexyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | n-hexyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| | 20 | n-hexyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | 21 | n-hexyl | Ph- | 7-(N)-morpholine |
| | 22 | n-hexyl | Ph- | 7-(N)-azetidine |
| | 23 | n-hexyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| | 24 | n-hexyl | Ph- | 7-(N)-pyrrolidine |
| | 25 | n-hexyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| | 26 | n-hexyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| | 27 | n-hexyl | Ph- | 7-(N)-N'-methylpiperazine |
| | 28 | n-hexyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | 29 | n-hexyl | Ph- | 7-NH-CBZ |
| | 30 | n-hexyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| | 31 | n-hexyl | Ph- | 7-NHC(O)CH ₂ Br |
| | 32 | n-hexyl | Ph- | 7-NH-C(NH)NH ₂ |
| | 33 | n-hexyl | Ph- | 7-(2)-thiophene |
| | 34 | n-hexyl | Ph- | 8-methyl |
| | 35 | n-hexyl | Ph- | 8-ethyl |
| | 36 | n-hexyl | Ph- | 8-iso-propyl |
| | 37 | n-hexyl | Ph- | 8-tert-butyl |

SRL 6071
(C-3021/2)

61

| | | | |
|----|---------|-----|--|
| 38 | n-hexyl | Ph- | 8-OH |
| 39 | n-hexyl | Ph- | 8-OCH ₃ |
| 40 | n-hexyl | Ph- | 8-O(iso-propyl) |
| 41 | n-hexyl | Ph- | 8-SCH ₃ |
| 42 | n-hexyl | Ph- | 8-SOCH ₃ |
| 43 | n-hexyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | n-hexyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | n-hexyl | Ph- | 8-NH ₂ |
| 46 | n-hexyl | Ph- | 8-NHOH |
| 47 | n-hexyl | Ph- | 8-NHCH ₃ |
| 48 | n-hexyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | n-hexyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | n-hexyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | n-hexyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | n-hexyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | n-hexyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | n-hexyl | Ph- | 8-(N)-morpholine |
| 55 | n-hexyl | Ph- | 8-(N)-azetidine |
| 56 | n-hexyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | n-hexyl | Ph- | 8-(N)-pyrrolidine |
| 58 | n-hexyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | n-hexyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | n-hexyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | n-hexyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | n-hexyl | Ph- | 8-NH-CBZ |
| 63 | n-hexyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | n-hexyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | n-hexyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | n-hexyl | Ph- | 8-(2)-thiophene |
| 67 | n-hexyl | Ph- | 9-methyl |
| 68 | n-hexyl | Ph- | 9-ethyl |
| 69 | n-hexyl | Ph- | 9-iso-propyl |
| 70 | n-hexyl | Ph- | 9-tert-butyl |
| 71 | n-hexyl | Ph- | 9-OH |
| 72 | n-hexyl | Ph- | 9-OCH ₃ |
| 73 | n-hexyl | Ph- | 9-O(iso-propyl) |
| 74 | n-hexyl | Ph- | 9-SCH ₃ |
| 75 | n-hexyl | Ph- | 9-SOCH ₃ |
| 76 | n-hexyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | n-hexyl | Ph- | 9-SCH ₂ CH ₃ |
| 78 | n-hexyl | Ph- | 9-NH ₂ |
| 79 | n-hexyl | Ph- | 9-NHOH |

SRL 6071
(C-3021/2)

62

| | | | |
|----------|---------|------------|--|
| 80 | n-hexyl | Ph- | 9-NHCH ₃ |
| 81 | n-hexyl | Ph- | 9-N(CH ₃) ₂ |
| 82 | n-hexyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | n-hexyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | n-hexyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | n-hexyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | n-hexyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | n-hexyl | Ph- | 9-(N)-morpholine |
| 88 | n-hexyl | Ph- | 9-(N)-azetidine |
| 89 | n-hexyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | n-hexyl | Ph- | 9-(N)-pyrrolidine |
| 91 | n-hexyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | n-hexyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | n-hexyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | n-hexyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | n-hexyl | Ph- | 9-NH-CBZ |
| 96 | n-hexyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | n-hexyl | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | n-hexyl | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | n-hexyl | Ph- | 9-(2)-thiophene |
| 100 | n-hexyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | n-hexyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | n-hexyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | n-hexyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |
| <hr/> | | | |
| F101.006 | 01 | iso-propyl | Ph- 7-methyl |
| | 02 | iso-propyl | Ph- 7-ethyl |
| | 03 | iso-propyl | Ph- 7-iso-propyl |
| | 04 | iso-propyl | Ph- 7-tert-butyl |
| | 05 | iso-propyl | Ph- 7-OH |
| | 06 | iso-propyl | Ph- 7-OCH ₃ |
| | 07 | iso-propyl | Ph- 7-O(iso-propyl) |
| | 08 | iso-propyl | Ph- 7-SCH ₃ |
| | 09 | iso-propyl | Ph- 7-SOCH ₃ |
| | 10 | iso-propyl | Ph- 7-SO ₂ CH ₃ |
| | 11 | iso-propyl | Ph- 7-SCH ₂ CH ₃ |
| | 12 | iso-propyl | Ph- 7-NH ₂ |
| | 13 | iso-propyl | Ph- 7-NHOH |
| | 14 | iso-propyl | Ph- 7-NHCH ₃ |
| | 15 | iso-propyl | Ph- 7-N(CH ₃) ₂ |
| | 16 | iso-propyl | Ph- 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | iso-propyl | Ph- 7-NHC(=O)CH ₃ |

SRL 6071
(C-3021/2)

63

| | | | |
|----|------------|-----|--|
| 18 | iso-propyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| 19 | iso-propyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| 20 | iso-propyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 21 | iso-propyl | Ph- | 7-(N)-morpholine |
| 22 | iso-propyl | Ph- | 7-(N)-azetidine |
| 23 | iso-propyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| 24 | iso-propyl | Ph- | 7-(N)-pyrrolidine |
| 25 | iso-propyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 26 | iso-propyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| 27 | iso-propyl | Ph- | 7-(N)-N'-methylpiperazine |
| 28 | iso-propyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| 29 | iso-propyl | Ph- | 7-NH-CBZ |
| 30 | iso-propyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| 31 | iso-propyl | Ph- | 7-NHC(O)CH ₂ Br |
| 32 | iso-propyl | Ph- | 7-NH-C(NH)NH ₂ |
| 33 | iso-propyl | Ph- | 7-(2)-thiophene |
| 34 | iso-propyl | Ph- | 8-methyl |
| 35 | iso-propyl | Ph- | 8-ethyl |
| 36 | iso-propyl | Ph- | 8-iso-propyl |
| 37 | iso-propyl | Ph- | 8-tert-butyl |
| 38 | iso-propyl | Ph- | 8-OH |
| 39 | iso-propyl | Ph- | 8-OCH ₃ |
| 40 | iso-propyl | Ph- | 8-O(iso-propyl) |
| 41 | iso-propyl | Ph- | 8-SCH ₃ |
| 42 | iso-propyl | Ph- | 8-SOCH ₃ |
| 43 | iso-propyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | iso-propyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | iso-propyl | Ph- | 8-NH ₂ |
| 46 | iso-propyl | Ph- | 8-NHOH |
| 47 | iso-propyl | Ph- | 8-NHCH ₃ |
| 48 | iso-propyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | iso-propyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | iso-propyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | iso-propyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | iso-propyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | iso-propyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | iso-propyl | Ph- | 8-(N)-morpholine |
| 55 | iso-propyl | Ph- | 8-(N)-azetidine |
| 56 | iso-propyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | iso-propyl | Ph- | 8-(N)-pyrrolidine |
| 58 | iso-propyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | iso-propyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |

SRL 6071
(C-3021/2)

64

| | | | |
|-----|------------|-----|--|
| 60 | iso-propyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | iso-propyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | iso-propyl | Ph- | 8-NH-CBZ |
| 63 | iso-propyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | iso-propyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | iso-propyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | iso-propyl | Ph- | 8-(2)-thiophene |
| 67 | iso-propyl | Ph- | 9-methyl |
| 68 | iso-propyl | Ph- | 9-ethyl |
| 69 | iso-propyl | Ph- | 9-iso-propyl |
| 70 | iso-propyl | Ph- | 9-tert-butyl |
| 71 | iso-propyl | Ph- | 9-OH |
| 72 | iso-propyl | Ph- | 9-OCH ₃ |
| 73 | iso-propyl | Ph- | 9-O(iso-propyl) |
| 74 | iso-propyl | Ph- | 9-SCH ₃ |
| 75 | iso-propyl | Ph- | 9-SOCH ₃ |
| 76 | iso-propyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | iso-propyl | Ph- | 9-SCH ₂ CH ₃ |
| 78 | iso-propyl | Ph- | 9-NH ₂ |
| 79 | iso-propyl | Ph- | 9-NHOH |
| 80 | iso-propyl | Ph- | 9-NHCH ₃ |
| 81 | iso-propyl | Ph- | 9-N(CH ₃) ₂ |
| 82 | iso-propyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | iso-propyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | iso-propyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | iso-propyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | iso-propyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | iso-propyl | Ph- | 9-(N)-morpholine |
| 88 | iso-propyl | Ph- | 9-(N)-azetidine |
| 89 | iso-propyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | iso-propyl | Ph- | 9-(N)-pyrrolidine |
| 91 | iso-propyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | iso-propyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | iso-propyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | iso-propyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | iso-propyl | Ph- | 9-NH-CBZ |
| 96 | iso-propyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | iso-propyl | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | iso-propyl | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | iso-propyl | Ph- | 9-(2)-thiophene |
| 100 | iso-propyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |

SRL 6071
(C-3021/2)

65

| | | | | |
|----------|-----|------------|-----|--|
| | 101 | iso-propyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| | 102 | iso-propyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| | 103 | iso-propyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |
| <hr/> | | | | |
| F101.007 | 01 | iso-butyl | Ph- | 7-methyl |
| | 02 | iso-butyl | Ph- | 7-ethyl |
| | 03 | iso-butyl | Ph- | 7-iso-propyl |
| | 04 | iso-butyl | Ph- | 7-tert-butyl |
| | 05 | iso-butyl | Ph- | 7-OH |
| | 06 | iso-butyl | Ph- | 7-OCH ₃ |
| | 07 | iso-butyl | Ph- | 7-O(iso-propyl) |
| | 08 | iso-butyl | Ph- | 7-SCH ₃ |
| | 09 | iso-butyl | Ph- | 7-SOCH ₃ |
| | 10 | iso-butyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | iso-butyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | iso-butyl | Ph- | 7-NH ₂ |
| | 13 | iso-butyl | Ph- | 7-NHOH |
| | 14 | iso-butyl | Ph- | 7-NHCH ₃ |
| | 15 | iso-butyl | Ph- | 7-N(CH ₃) ₂ |
| | 16 | iso-butyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | iso-butyl | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | iso-butyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | iso-butyl | Ph- | 7-NMeCH ₂ CO ₂ H |
| | 20 | iso-butyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | 21 | iso-butyl | Ph- | 7-(N)-morpholine |
| | 22 | iso-butyl | Ph- | 7-(N)-azetidine |
| | 23 | iso-butyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| | 24 | iso-butyl | Ph- | 7-(N)-pyrrolidine |
| | 25 | iso-butyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| | 26 | iso-butyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| | 27 | iso-butyl | Ph- | 7-(N)-N'-methylpiperazine |
| | 28 | iso-butyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | 29 | iso-butyl | Ph- | 7-NH-CBZ |
| | 30 | iso-butyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| | 31 | iso-butyl | Ph- | 7-NHC(O)CH ₂ Br |
| | 32 | iso-butyl | Ph- | 7-NH-C(NH)NH ₂ |
| | 33 | iso-butyl | Ph- | 7-(2)-thiophene |
| | 34 | iso-butyl | Ph- | 8-methyl |
| | 35 | iso-butyl | Ph- | 8-ethyl |
| | 36 | iso-butyl | Ph- | 8-iso-propyl |
| | 37 | iso-butyl | Ph- | 8-tert-butyl |
| | 38 | iso-butyl | Ph- | 8-OH |
| | 39 | iso-butyl | Ph- | 8-OCH ₃ |

SRL 6071
(C-3021/2)

66

| | | | |
|----|-----------|-----|--|
| 40 | iso-butyl | Ph- | 8-O(iso-propyl) |
| 41 | iso-butyl | Ph- | 8-SCH ₃ |
| 42 | iso-butyl | Ph- | 8-SOCH ₃ |
| 43 | iso-butyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | iso-butyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | iso-butyl | Ph- | 8-NH ₂ |
| 46 | iso-butyl | Ph- | 8-NHOH |
| 47 | iso-butyl | Ph- | 8-NHCH ₃ |
| 48 | iso-butyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | iso-butyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | iso-butyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | iso-butyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | iso-butyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | iso-butyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | iso-butyl | Ph- | 8-(N)-morpholine |
| 55 | iso-butyl | Ph- | 8-(N)-azetidine |
| 56 | iso-butyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | iso-butyl | Ph- | 8-(N)-pyrrolidine |
| 58 | iso-butyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | iso-butyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | iso-butyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | iso-butyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | iso-butyl | Ph- | 8-NH-CBZ |
| 63 | iso-butyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | iso-butyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | iso-butyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | iso-butyl | Ph- | 8-(2)-thiophene |
| 67 | iso-butyl | Ph- | 9-methyl |
| 68 | iso-butyl | Ph- | 9-ethyl |
| 69 | iso-butyl | Ph- | 9-iso-propyl |
| 70 | iso-butyl | Ph- | 9-tert-butyl |
| 71 | iso-butyl | Ph- | 9-OH |
| 72 | iso-butyl | Ph- | 9-OCH ₃ |
| 73 | iso-butyl | Ph- | 9-O(iso-propyl) |
| 74 | iso-butyl | Ph- | 9-SCH ₃ |
| 75 | iso-butyl | Ph- | 9-SOCH ₃ |
| 76 | iso-butyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | iso-butyl | Ph- | 9-SCH ₂ CH ₃ |
| 78 | iso-butyl | Ph- | 9-NH ₂ |
| 79 | iso-butyl | Ph- | 9-NHOH |
| 80 | iso-butyl | Ph- | 9-NHCH ₃ |
| 81 | iso-butyl | Ph- | 9-N(CH ₃) ₂ |

SRL 6071
(C-3021/2)

67

| | | | |
|-----|-----------|-----|--|
| 82 | iso-butyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | iso-butyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | iso-butyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | iso-butyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | iso-butyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | iso-butyl | Ph- | 9-(N)-morpholine |
| 88 | iso-butyl | Ph- | 9-(N)-azetidine |
| 89 | iso-butyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | iso-butyl | Ph- | 9-(N)-pyrrolidine |
| 91 | iso-butyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | iso-butyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | iso-butyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | iso-butyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | iso-butyl | Ph- | 9-NH-CBZ |
| 96 | iso-butyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | iso-butyl | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | iso-butyl | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | iso-butyl | Ph- | 9-(2)-thiophene |
| 100 | iso-butyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | iso-butyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | iso-butyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | iso-butyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |

| | | | | |
|----------|----|------------|-----|---|
| F101.008 | 01 | iso-pentyl | Ph- | 7-methyl |
| | 02 | iso-pentyl | Ph- | 7-ethyl |
| | 03 | iso-pentyl | Ph- | 7-iso-propyl |
| | 04 | iso-pentyl | Ph- | 7-tert-butyl |
| | 05 | iso-pentyl | Ph- | 7-OH |
| | 06 | iso-pentyl | Ph- | 7-OCH ₃ |
| | 07 | iso-pentyl | Ph- | 7-O(iso-propyl) |
| | 08 | iso-pentyl | Ph- | 7-SCH ₃ |
| | 09 | iso-pentyl | Ph- | 7-SOCH ₃ |
| | 10 | iso-pentyl | Ph- | 7-SO ₂ CH ₃ |
| | 11 | iso-pentyl | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | iso-pentyl | Ph- | 7-NH ₂ |
| | 13 | iso-pentyl | Ph- | 7-NHOH |
| | 14 | iso-pentyl | Ph- | 7-NHCH ₃ |
| | 15 | iso-pentyl | Ph- | 7-N(CH ₃) ₂ |
| | 16 | iso-pentyl | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | iso-pentyl | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | iso-pentyl | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | iso-pentyl | Ph- | 7-NMeCH ₂ CO ₂ H |

SRL 6071
(C-3021/2)

68

| | | | |
|----|------------|-----|--|
| 20 | iso-pentyl | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 21 | iso-pentyl | Ph- | 7-(N)-morpholine |
| 22 | iso-pentyl | Ph- | 7-(N)-azetidine |
| 23 | iso-pentyl | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| 24 | iso-pentyl | Ph- | 7-(N)-pyrrolidine |
| 25 | iso-pentyl | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 26 | iso-pentyl | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| 27 | iso-pentyl | Ph- | 7-(N)-N'-methylpiperazine |
| 28 | iso-pentyl | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| 29 | iso-pentyl | Ph- | 7-NH-CBZ |
| 30 | iso-pentyl | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| 31 | iso-pentyl | Ph- | 7-NHC(O)CH ₂ Br |
| 32 | iso-pentyl | Ph- | 7-NH-C(NH)NH ₂ |
| 33 | iso-pentyl | Ph- | 7-(2)-thiophene |
| 34 | iso-pentyl | Ph- | 8-methyl |
| 35 | iso-pentyl | Ph- | 8-ethyl |
| 36 | iso-pentyl | Ph- | 8-iso-propyl |
| 37 | iso-pentyl | Ph- | 8-tert-butyl |
| 38 | iso-pentyl | Ph- | 8-OH |
| 39 | iso-pentyl | Ph- | 8-OCH ₃ |
| 40 | iso-pentyl | Ph- | 8-O(iso-propyl) |
| 41 | iso-pentyl | Ph- | 8-SCH ₃ |
| 42 | iso-pentyl | Ph- | 8-SOCH ₃ |
| 43 | iso-pentyl | Ph- | 8-SO ₂ CH ₃ |
| 44 | iso-pentyl | Ph- | 8-SCH ₂ CH ₃ |
| 45 | iso-pentyl | Ph- | 8-NH ₂ |
| 46 | iso-pentyl | Ph- | 8-NHOH |
| 47 | iso-pentyl | Ph- | 8-NHCH ₃ |
| 48 | iso-pentyl | Ph- | 8-N(CH ₃) ₂ |
| 49 | iso-pentyl | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | iso-pentyl | Ph- | 8-NHC(=O)CH ₃ |
| 51 | iso-pentyl | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | iso-pentyl | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | iso-pentyl | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | iso-pentyl | Ph- | 8-(N)-morpholine |
| 55 | iso-pentyl | Ph- | 8-(N)-azetidine |
| 56 | iso-pentyl | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | iso-pentyl | Ph- | 8-(N)-pyrrolidine |
| 58 | iso-pentyl | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | iso-pentyl | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | iso-pentyl | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | iso-pentyl | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |

SRL 6071
(C-3021/2)

69

| | | | |
|-----|------------|-----|--|
| 62 | iso-pentyl | Ph- | 8-NH-CBZ |
| 63 | iso-pentyl | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | iso-pentyl | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | iso-pentyl | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | iso-pentyl | Ph- | 8-(2)-thiophene |
| 67 | iso-pentyl | Ph- | 9-methyl |
| 68 | iso-pentyl | Ph- | 9-ethyl |
| 69 | iso-pentyl | Ph- | 9-iso-propyl |
| 70 | iso-pentyl | Ph- | 9-tert-butyl |
| 71 | iso-pentyl | Ph- | 9-OH |
| 72 | iso-pentyl | Ph- | 9-OCH ₃ |
| 73 | iso-pentyl | Ph- | 9-O(iso-propyl) |
| 74 | iso-pentyl | Ph- | 9-SCH ₃ |
| 75 | iso-pentyl | Ph- | 9-SOCH ₃ |
| 76 | iso-pentyl | Ph- | 9-SO ₂ CH ₃ |
| 77 | iso-pentyl | Ph- | 9-SCH ₂ CH ₃ |
| 78 | iso-pentyl | Ph- | 9-NH ₂ |
| 79 | iso-pentyl | Ph- | 9-NHOH |
| 80 | iso-pentyl | Ph- | 9-NHCH ₃ |
| 81 | iso-pentyl | Ph- | 9-N(CH ₃) ₂ |
| 82 | iso-pentyl | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | iso-pentyl | Ph- | 9-NHC(=O)CH ₃ |
| 84 | iso-pentyl | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | iso-pentyl | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | iso-pentyl | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | iso-pentyl | Ph- | 9-(N)-morpholine |
| 88 | iso-pentyl | Ph- | 9-(N)-azetidine |
| 89 | iso-pentyl | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | iso-pentyl | Ph- | 9-(N)-pyrrolidine |
| 91 | iso-pentyl | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | iso-pentyl | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | iso-pentyl | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | iso-pentyl | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | iso-pentyl | Ph- | 9-NH-CBZ |
| 96 | iso-pentyl | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | iso-pentyl | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | iso-pentyl | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | iso-pentyl | Ph- | 9-(2)-thiophene |
| 100 | iso-pentyl | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | iso-pentyl | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | iso-pentyl | Ph- | 7-SCH ₃ , 8-SCH ₃ |

SRL 6071
(C-3021/2)

70

| | 103 | iso-pentyl | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |
|----------|-----|--|-----|--|
| F101.009 | 01 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-methyl |
| | 02 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-ethyl |
| | 03 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-iso-propyl |
| | 04 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-tert-butyl |
| | 05 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-OH |
| | 06 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-OCH ₃ |
| | 07 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-O(iso-propyl) |
| | 08 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-SCH ₃ |
| | 09 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-SOCH ₃ |
| | 10 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-SO ₂ CH ₃ |
| | 11 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NH ₂ |
| | 13 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NHOH |
| | 14 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NHCH ₃ |
| | 15 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-N(CH ₃) ₂ |
| | 16 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NMeCH ₂ CO ₂ H |
| | 20 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | 21 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-morpholine |
| | 22 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-azetidine |
| | 23 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| | 24 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-pyrrolidine |
| | 25 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| | 26 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| | 27 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-N'-methylpiperazine |
| | 28 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | 29 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NH-CBZ |
| | 30 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| | 31 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NHC(O)CH ₂ Br |
| | 32 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-NH-C(NH)NH ₂ |
| | 33 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 7-(2)-thiophene |
| | 34 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 8-methyl |
| | 35 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 8-ethyl |
| | 36 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 8-iso-propyl |
| | 37 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 8-tert-butyl |
| | 38 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 8-OH |
| | 39 | CH ₂ C(=O)C ₂ H ₅ | Ph- | 8-OCH ₃ |

SRL 6071
(C-3021/2)

71

| | | | |
|----|--|-----|--|
| 40 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-O(iso-propyl) |
| 41 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-SCH ₃ |
| 42 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-SOCH ₃ |
| 43 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-SO ₂ CH ₃ |
| 44 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-SCH ₂ CH ₃ |
| 45 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NH ₂ |
| 46 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NHOH |
| 47 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NHCH ₃ |
| 48 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-N(CH ₃) ₂ |
| 49 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NHC(=O)CH ₃ |
| 51 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-morpholine |
| 55 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-azetidine |
| 56 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-pyrrolidine |
| 58 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NH-CBZ |
| 63 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 8-(2)-thiophene |
| 67 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-methyl |
| 68 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-ethyl |
| 69 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-iso-propyl |
| 70 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-tert-butyl |
| 71 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-OH |
| 72 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-OCH ₃ |
| 73 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-O(iso-propyl) |
| 74 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-SCH ₃ |
| 75 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-SOCH ₃ |
| 76 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-SO ₂ CH ₃ |
| 77 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-SCH ₂ CH ₃ |
| 78 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NH ₂ |
| 79 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NHOH |
| 80 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NHCH ₃ |

SRL 6071
(C-3021/2)

72

| | | | |
|-----|--|-----|--|
| 81 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-N(CH ₃) ₂ |
| 82 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NHC(=O)CH ₃ |
| 84 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-morpholine |
| 88 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-azetidine |
| 89 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-pyrrolidine |
| 91 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NH-CBZ |
| 96 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 9-(2)-thiophene |
| 100 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | $\text{CH}_2\text{C}(=\text{O})\text{C}_2\text{H}_5$ | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |

| | | | | |
|----------|----|------------------------------------|-----|---|
| F101.010 | 01 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-methyl |
| | 02 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-ethyl |
| | 03 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-iso-propyl |
| | 04 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-tert-butyl |
| | 05 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-OH |
| | 06 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-OCH ₃ |
| | 07 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-O(iso-propyl) |
| | 08 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-SCH ₃ |
| | 09 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-SOCH ₃ |
| | 10 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-SO ₂ CH ₃ |
| | 11 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-NH ₂ |
| | 13 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-NHOH |
| | 14 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-NHCH ₃ |
| | 15 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-N(CH ₃) ₂ |
| | 16 | $\text{CH}_2\text{OC}_2\text{H}_5$ | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |

SRL 6071
(C-3021/2)

73

| | | | |
|----|--|-----|--|
| 17 | CH ₂ OC ₂ H ₅ | Ph- | 7-NHC(=O)CH ₃ |
| 18 | CH ₂ OC ₂ H ₅ | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| 19 | CH ₂ OC ₂ H ₅ | Ph- | 7-NMeCH ₂ CO ₂ H |
| 20 | CH ₂ OC ₂ H ₅ | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 21 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-morpholine |
| 22 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-azetidine |
| 23 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| 24 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-pyrrolidine |
| 25 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 26 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| 27 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-N'-methylpiperazine |
| 28 | CH ₂ OC ₂ H ₅ | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| 29 | CH ₂ OC ₂ H ₅ | Ph- | 7-NH-CBZ |
| 30 | CH ₂ OC ₂ H ₅ | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| 31 | CH ₂ OC ₂ H ₅ | Ph- | 7-NHC(O)CH ₂ Br |
| 32 | CH ₂ OC ₂ H ₅ | Ph- | 7-NH-C(NH)NH ₂ |
| 33 | CH ₂ OC ₂ H ₅ | Ph- | 7-(2)-thiophene |
| 34 | CH ₂ OC ₂ H ₅ | Ph- | 8-methyl |
| 35 | CH ₂ OC ₂ H ₅ | Ph- | 8-ethyl |
| 36 | CH ₂ OC ₂ H ₅ | Ph- | 8-iso-propyl |
| 37 | CH ₂ OC ₂ H ₅ | Ph- | 8-tert-butyl |
| 38 | CH ₂ OC ₂ H ₅ | Ph- | 8-OH |
| 39 | CH ₂ OC ₂ H ₅ | Ph- | 8-OCH ₃ |
| 40 | CH ₂ OC ₂ H ₅ | Ph- | 8-O(iso-propyl) |
| 41 | CH ₂ OC ₂ H ₅ | Ph- | 8-SCH ₃ |
| 42 | CH ₂ OC ₂ H ₅ | Ph- | 8-SOCH ₃ |
| 43 | CH ₂ OC ₂ H ₅ | Ph- | 8-SO ₂ CH ₃ |
| 44 | CH ₂ OC ₂ H ₅ | Ph- | 8-SCH ₂ CH ₃ |
| 45 | CH ₂ OC ₂ H ₅ | Ph- | 8-NH ₂ |
| 46 | CH ₂ OC ₂ H ₅ | Ph- | 8-NHOH |
| 47 | CH ₂ OC ₂ H ₅ | Ph- | 8-NHCH ₃ |
| 48 | CH ₂ OC ₂ H ₅ | Ph- | 8-N(CH ₃) ₂ |
| 49 | CH ₂ OC ₂ H ₅ | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | CH ₂ OC ₂ H ₅ | Ph- | 8-NHC(=O)CH ₃ |
| 51 | CH ₂ OC ₂ H ₅ | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | CH ₂ OC ₂ H ₅ | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | CH ₂ OC ₂ H ₅ | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-morpholine |
| 55 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-azetidine |
| 56 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |

SRL 6071
(C-3021/2)

74

| | | | |
|----|--|-----|--|
| 57 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-pyrrolidine |
| 58 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | CH ₂ OC ₂ H ₅ | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | CH ₂ OC ₂ H ₅ | Ph- | 8-NH-CBZ |
| 63 | CH ₂ OC ₂ H ₅ | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | CH ₂ OC ₂ H ₅ | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | CH ₂ OC ₂ H ₅ | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | CH ₂ OC ₂ H ₅ | Ph- | 8-(2)-thiophene |
| 67 | CH ₂ OC ₂ H ₅ | Ph- | 9-methyl |
| 68 | CH ₂ OC ₂ H ₅ | Ph- | 9-ethyl |
| 69 | CH ₂ OC ₂ H ₅ | Ph- | 9-iso-propyl |
| 70 | CH ₂ OC ₂ H ₅ | Ph- | 9-tert-butyl |
| 71 | CH ₂ OC ₂ H ₅ | Ph- | 9-OH |
| 72 | CH ₂ OC ₂ H ₅ | Ph- | 9-OCH ₃ |
| 73 | CH ₂ OC ₂ H ₅ | Ph- | 9-O(iso-propyl) |
| 74 | CH ₂ OC ₂ H ₅ | Ph- | 9-SCH ₃ |
| 75 | CH ₂ OC ₂ H ₅ | Ph- | 9-SOCH ₃ |
| 76 | CH ₂ OC ₂ H ₅ | Ph- | 9-SO ₂ CH ₃ |
| 77 | CH ₂ OC ₂ H ₅ | Ph- | 9-SCH ₂ CH ₃ |
| 78 | CH ₂ OC ₂ H ₅ | Ph- | 9-NH ₂ |
| 79 | CH ₂ OC ₂ H ₅ | Ph- | 9-NHOH |
| 80 | CH ₂ OC ₂ H ₅ | Ph- | 9-NHCH ₃ |
| 81 | CH ₂ OC ₂ H ₅ | Ph- | 9-N(CH ₃) ₂ |
| 82 | CH ₂ OC ₂ H ₅ | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | CH ₂ OC ₂ H ₅ | Ph- | 9-NHC(=O)CH ₃ |
| 84 | CH ₂ OC ₂ H ₅ | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | CH ₂ OC ₂ H ₅ | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | CH ₂ OC ₂ H ₅ | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-morpholine |
| 88 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-azetidine |
| 89 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-pyrrolidine |
| 91 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | CH ₂ OC ₂ H ₅ | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | CH ₂ OC ₂ H ₅ | Ph- | 9-NH-CBZ |
| 96 | CH ₂ OC ₂ H ₅ | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | CH ₂ OC ₂ H ₅ | Ph- | 9-NHC(O)CH ₂ Br |

SRL 6071
(C-3021/2)

75

| | | | | |
|----------|-----|---|-----|--|
| | 98 | CH ₂ OC ₂ H ₅ | Ph- | 9-NH-C(NH)NH ₂ |
| | 99 | CH ₂ OC ₂ H ₅ | Ph- | 9-(2)-thiophene |
| | 100 | CH ₂ OC ₂ H ₅ | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| | 101 | CH ₂ OC ₂ H ₅ | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| | 102 | CH ₂ OC ₂ H ₅ | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| | 103 | CH ₂ OC ₂ H ₅ | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |
| <hr/> | | | | |
| F101.011 | 01 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-methyl |
| | 02 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-ethyl |
| | 03 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-iso-propyl |
| | 04 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-tert-butyl |
| | 05 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-OH |
| | 06 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-OCH ₃ |
| | 07 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-O(iso-propyl) |
| | 08 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-SCH ₃ |
| | 09 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-SOCH ₃ |
| | 10 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-SO ₂ CH ₃ |
| | 11 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-SCH ₂ CH ₃ |
| | 12 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NH ₂ |
| | 13 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NHOH |
| | 14 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NHCH ₃ |
| | 15 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-N(CH ₃) ₂ |
| | 16 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | 17 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NHC(=O)CH ₃ |
| | 18 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| | 19 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NMeCH ₂ CO ₂ H |
| | 20 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | 21 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-morpholine |
| | 22 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-azetidine |
| | 23 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| | 24 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-pyrrolidine |
| | 25 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| | 26 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| | 27 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-N'-methylpiperazine |
| | 28 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | 29 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NH-CBZ |
| | 30 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| | 31 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NHC(O)CH ₂ Br |
| | 32 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-NH-C(NH)NH ₂ |
| | 33 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-(2)-thiophene |

SRL 6071
(C-3021/2)

76

| | | | |
|----|---|-----|--|
| 34 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-methyl |
| 35 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-ethyl |
| 36 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-iso-propyl |
| 37 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-tert-butyl |
| 38 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-OH |
| 39 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-OCH ₃ |
| 40 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-O(iso-propyl) |
| 41 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-SCH ₃ |
| 42 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-SOCH ₃ |
| 43 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-SO ₂ CH ₃ |
| 44 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-SCH ₂ CH ₃ |
| 45 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NH ₂ |
| 46 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NHOH |
| 47 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NHCH ₃ |
| 48 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-N(CH ₃) ₂ |
| 49 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NHC(=O)CH ₃ |
| 51 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-N(CH ₂ CH ₃) ₂ |
| 52 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-morpholine |
| 55 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-azetidine |
| 56 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-pyrrolidine |
| 58 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NH-CBZ |
| 63 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 8-(2)-thiophene |
| 67 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-methyl |
| 68 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-ethyl |
| 69 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-iso-propyl |
| 70 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-tert-butyl |
| 71 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-OH |
| 72 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-OCH ₃ |
| 73 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-O(iso-propyl) |
| 74 | $\text{CH}_2\text{CH}(\text{OH})\text{C}_2\text{H}_5$ | Ph- | 9-SCH ₃ |

SRL 6071
(C-3021/2)

77

| | | | |
|-----|---|-----|--|
| 75 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-SOCH ₃ |
| 76 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-SO ₂ CH ₃ |
| 77 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-SCH ₂ CH ₃ |
| 78 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NH ₂ |
| 79 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NHOH |
| 80 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NHCH ₃ |
| 81 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-N(CH ₃) ₂ |
| 82 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NHC(=O)CH ₃ |
| 84 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-morpholine |
| 88 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-azetidine |
| 89 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-pyrrolidine |
| 91 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 92 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NH-CBZ |
| 96 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 9-(2)-thiophene |
| 100 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | CH ₂ CH(OH)C ₂ H ₅ | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |

| | | | | |
|----------|----|--------------------------------|-----|------------------------------------|
| F101.012 | 01 | CH ₂ O-(4-picoline) | Ph- | 7-methyl |
| | 02 | CH ₂ O-(4-picoline) | Ph- | 7-ethyl |
| | 03 | CH ₂ O-(4-picoline) | Ph- | 7-iso-propyl |
| | 04 | CH ₂ O-(4-picoline) | Ph- | 7-tert-butyl |
| | 05 | CH ₂ O-(4-picoline) | Ph- | 7-OH |
| | 06 | CH ₂ O-(4-picoline) | Ph- | 7-OCH ₃ |
| | 07 | CH ₂ O-(4-picoline) | Ph- | 7-O(iso-propyl) |
| | 08 | CH ₂ O-(4-picoline) | Ph- | 7-SCH ₃ |
| | 09 | CH ₂ O-(4-picoline) | Ph- | 7-SOCH ₃ |
| | 10 | CH ₂ O-(4-picoline) | Ph- | 7-SO ₂ CH ₃ |
| | 11 | CH ₂ O-(4-picoline) | Ph- | 7-SCH ₂ CH ₃ |

SRL 6071
(C-3021/2)

78

| | | | |
|----|--------------------------------|-----|--|
| 12 | CH ₂ O-(4-picoline) | Ph- | 7-NH ₂ |
| 13 | CH ₂ O-(4-picoline) | Ph- | 7-NHOH |
| 14 | CH ₂ O-(4-picoline) | Ph- | 7-NHCH ₃ |
| 15 | CH ₂ O-(4-picoline) | Ph- | 7-N(CH ₃) ₂ |
| 16 | CH ₂ O-(4-picoline) | Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| 17 | CH ₂ O-(4-picoline) | Ph- | 7-NHC(=O)CH ₃ |
| 18 | CH ₂ O-(4-picoline) | Ph- | 7-N(CH ₂ CH ₃) ₂ |
| 19 | CH ₂ O-(4-picoline) | Ph- | 7-NMeCH ₂ CO ₂ H |
| 20 | CH ₂ O-(4-picoline) | Ph- | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 21 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-morpholine |
| 22 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-azetidine |
| 23 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-N-methylazetidinium, I ⁻ |
| 24 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-pyrrolidine |
| 25 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 26 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-N-methyl-morpholinium, I ⁻ |
| 27 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-N'-methylpiperazine |
| 28 | CH ₂ O-(4-picoline) | Ph- | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| 29 | CH ₂ O-(4-picoline) | Ph- | 7-NH-CBZ |
| 30 | CH ₂ O-(4-picoline) | Ph- | 7-NHC(O)C ₅ H ₁₁ |
| 31 | CH ₂ O-(4-picoline) | Ph- | 7-NHC(O)CH ₂ Br |
| 32 | CH ₂ O-(4-picoline) | Ph- | 7-NH-C(NH)NH ₂ |
| 33 | CH ₂ O-(4-picoline) | Ph- | 7-(2)-thiophene |
| 34 | CH ₂ O-(4-picoline) | Ph- | 8-methyl |
| 35 | CH ₂ O-(4-picoline) | Ph- | 8-ethyl |
| 36 | CH ₂ O-(4-picoline) | Ph- | 8-iso-propyl |
| 37 | CH ₂ O-(4-picoline) | Ph- | 8-tert-butyl |
| 38 | CH ₂ O-(4-picoline) | Ph- | 8-OH |
| 39 | CH ₂ O-(4-picoline) | Ph- | 8-OCH ₃ |
| 40 | CH ₂ O-(4-picoline) | Ph- | 8-O(iso-propyl) |
| 41 | CH ₂ O-(4-picoline) | Ph- | 8-SCH ₃ |
| 42 | CH ₂ O-(4-picoline) | Ph- | 8-SOCH ₃ |
| 43 | CH ₂ O-(4-picoline) | Ph- | 8-SO ₂ CH ₃ |
| 44 | CH ₂ O-(4-picoline) | Ph- | 8-SCH ₂ CH ₃ |
| 45 | CH ₂ O-(4-picoline) | Ph- | 8-NH ₂ |
| 46 | CH ₂ O-(4-picoline) | Ph- | 8-NHOH |
| 47 | CH ₂ O-(4-picoline) | Ph- | 8-NHCH ₃ |
| 48 | CH ₂ O-(4-picoline) | Ph- | 8-N(CH ₃) ₂ |
| 49 | CH ₂ O-(4-picoline) | Ph- | 8-N ⁺ (CH ₃) ₃ , I ⁻ |
| 50 | CH ₂ O-(4-picoline) | Ph- | 8-NHC(=O)CH ₃ |
| 51 | CH ₂ O-(4-picoline) | Ph- | 8-N(CH ₂ CH ₃) ₂ |

SRL 6071
(C-3021/2)

79

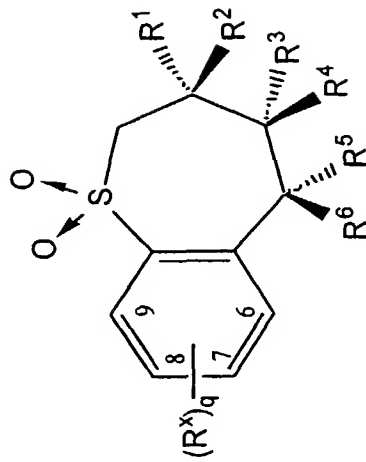
| | | | |
|----|--------------------------------|-----|--|
| 52 | CH ₂ O-(4-picoline) | Ph- | 8-NMeCH ₂ CO ₂ H |
| 53 | CH ₂ O-(4-picoline) | Ph- | 8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 54 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-morpholine |
| 55 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-azetidine |
| 56 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-N-methylazetidinium, I ⁻ |
| 57 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-pyrrolidine |
| 58 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-N-methyl-pyrrolidinium, I ⁻ |
| 59 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-N-methyl-morpholinium, I ⁻ |
| 60 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-N'-methylpiperazine |
| 61 | CH ₂ O-(4-picoline) | Ph- | 8-(N)-N'-dimethylpiperazinium, I ⁻ |
| 62 | CH ₂ O-(4-picoline) | Ph- | 8-NH-CBZ |
| 63 | CH ₂ O-(4-picoline) | Ph- | 8-NHC(O)C ₅ H ₁₁ |
| 64 | CH ₂ O-(4-picoline) | Ph- | 8-NHC(O)CH ₂ Br |
| 65 | CH ₂ O-(4-picoline) | Ph- | 8-NH-C(NH)NH ₂ |
| 66 | CH ₂ O-(4-picoline) | Ph- | 8-(2)-thiophene |
| 67 | CH ₂ O-(4-picoline) | Ph- | 9-methyl |
| 68 | CH ₂ O-(4-picoline) | Ph- | 9-ethyl |
| 69 | CH ₂ O-(4-picoline) | Ph- | 9-iso-propyl |
| 70 | CH ₂ O-(4-picoline) | Ph- | 9-tert-butyl |
| 71 | CH ₂ O-(4-picoline) | Ph- | 9-OH |
| 72 | CH ₂ O-(4-picoline) | Ph- | 9-OCH ₃ |
| 73 | CH ₂ O-(4-picoline) | Ph- | 9-O(iso-propyl) |
| 74 | CH ₂ O-(4-picoline) | Ph- | 9-SCH ₃ |
| 75 | CH ₂ O-(4-picoline) | Ph- | 9-SOCH ₃ |
| 76 | CH ₂ O-(4-picoline) | Ph- | 9-SO ₂ CH ₃ |
| 77 | CH ₂ O-(4-picoline) | Ph- | 9-SCH ₂ CH ₃ |
| 78 | CH ₂ O-(4-picoline) | Ph- | 9-NH ₂ |
| 79 | CH ₂ O-(4-picoline) | Ph- | 9-NHOH |
| 80 | CH ₂ O-(4-picoline) | Ph- | 9-NHCH ₃ |
| 81 | CH ₂ O-(4-picoline) | Ph- | 9-N(CH ₃) ₂ |
| 82 | CH ₂ O-(4-picoline) | Ph- | 9-N ⁺ (CH ₃) ₃ , I ⁻ |
| 83 | CH ₂ O-(4-picoline) | Ph- | 9-NHC(=O)CH ₃ |
| 84 | CH ₂ O-(4-picoline) | Ph- | 9-N(CH ₂ CH ₃) ₂ |
| 85 | CH ₂ O-(4-picoline) | Ph- | 9-NMeCH ₂ CO ₂ H |
| 86 | CH ₂ O-(4-picoline) | Ph- | 9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| 87 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-morpholine |
| 88 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-azetidine |
| 89 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-N-methylazetidinium, I ⁻ |
| 90 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-pyrrolidine |
| 91 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-N-methyl-pyrrolidinium, I ⁻ |

SRL 6071
(C-3021/2)

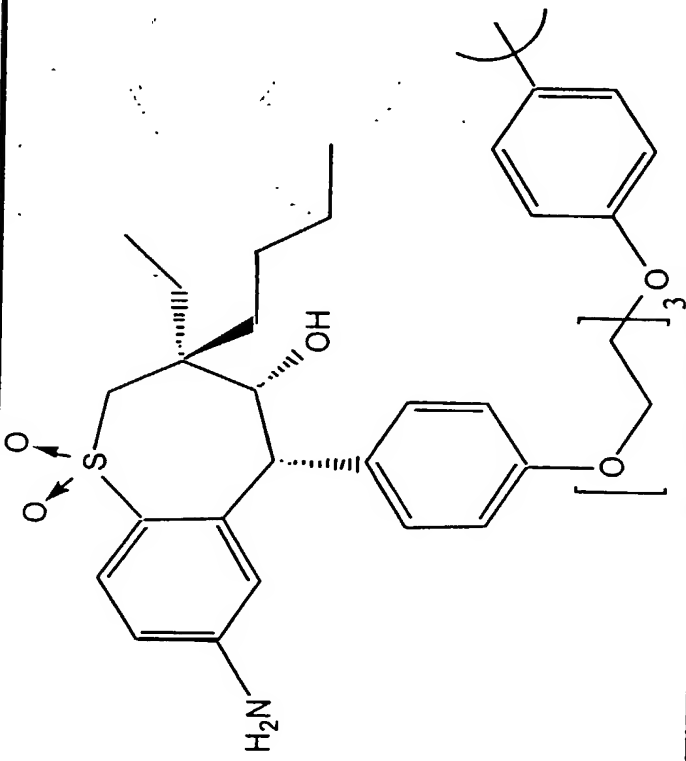
80

| | | | |
|-----|--------------------------------|-----|--|
| 92 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-N-methyl-morpholinium, I ⁻ |
| 93 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-N'-methylpiperazine |
| 93 | CH ₂ O-(4-picoline) | Ph- | 9-(N)-N'-dimethylpiperazinium, I ⁻ |
| 95 | CH ₂ O-(4-picoline) | Ph- | 9-NH-CBZ |
| 96 | CH ₂ O-(4-picoline) | Ph- | 9-NHC(O)C ₅ H ₁₁ |
| 97 | CH ₂ O-(4-picoline) | Ph- | 9-NHC(O)CH ₂ Br |
| 98 | CH ₂ O-(4-picoline) | Ph- | 9-NH-C(NH)NH ₂ |
| 99 | CH ₂ O-(4-picoline) | Ph- | 9-(2)-thiophene |
| 100 | CH ₂ O-(4-picoline) | Ph- | 7-OCH ₃ , 8-OCH ₃ |
| 101 | CH ₂ O-(4-picoline) | Ph- | 7-SCH ₃ , 8-OCH ₃ |
| 102 | CH ₂ O-(4-picoline) | Ph- | 7-SCH ₃ , 8-SCH ₃ |
| 103 | CH ₂ O-(4-picoline) | Ph- | 6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃ |

Additional Structures of the Present Invention



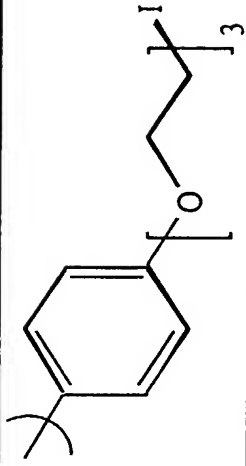
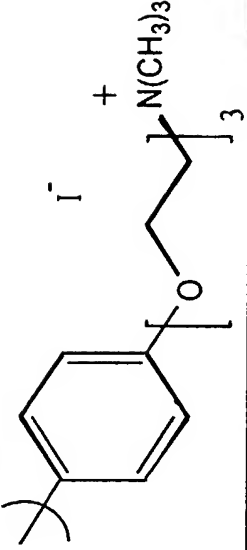
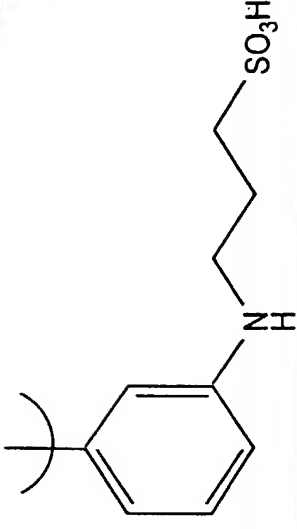
| Compound Number | R ¹ | R ² | R ³ | R ⁴ | R ⁵ |
|-----------------|----------------|----------------|----------------|----------------|--------------------|
| 101 | ethyl | n-butyl | OH | H | phenyl |
| 102 | ethyl | n-butyl | OH | H | phenyl |
| 103 | n-butyl | ethyl | OH | H | phenyl |
| 104 | ethyl | n-butyl | OH | H | phenyl |
| 105 | ethyl | n-butyl | OH | H | phenyl |
| 106 | ethyl | n-butyl | OH | H | phenyl |
| 107 | n-butyl | ethyl | OH | H | 4-(decyloxy)phenyl |
| 108 | ethyl | n-butyl | OH | H | phenyl |
| 109 | ethyl | n-butyl | OH | H | 4-(decyloxy)phenyl |
| 110 | ethyl | n-butyl | OH | H | phenyl |
| 111 | n-butyl | ethyl | OH | H | 4-hydroxyphenyl |

| II2 | ethyl | n-butyl | OH | H |  |
|-----|---------|---------|----|---|--|
| II3 | ethyl | n-butyl | OH | H | 4-hydroxyphenyl |
| II4 | ethyl | n-butyl | OH | H | 4-methoxyphenyl |
| II5 | n-butyl | ethyl | OH | H | 4-methoxyphenyl |
| II6 | ethyl | n-butyl | OH | H | 4-methoxyphenyl |
| II7 | n-butyl | ethyl | OH | H | phenyl |
| II8 | ethyl | n-butyl | OH | H | phenyl |
| II9 | ethyl | n-butyl | OH | H | phenyl |
| I20 | n-butyl | ethyl | OH | H | phenyl |
| I21 | ethyl | n-butyl | OH | H | phenyl |
| I22 | n-butyl | ethyl | OH | H | phenyl |

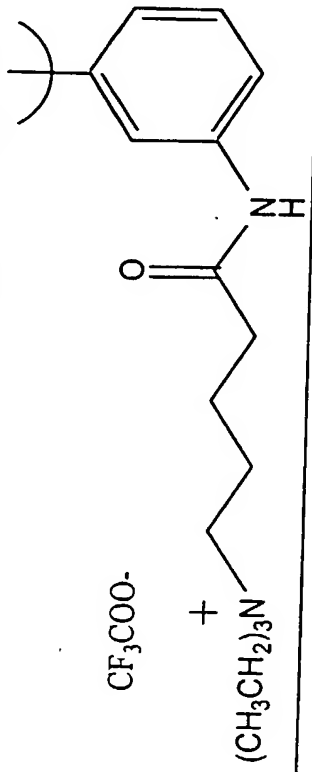
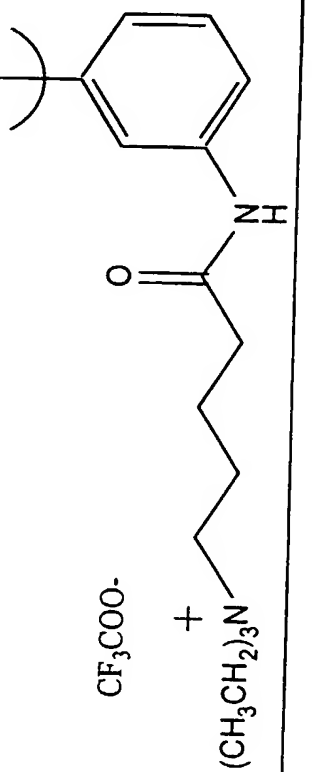
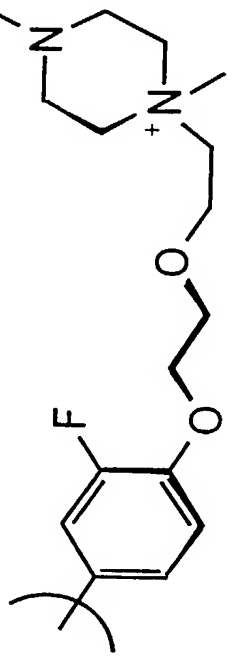
| | | | | | |
|-----|---------|---------|----|----|-------------------------|
| 123 | ethyl | n-butyl | OH | H | phenyl |
| 124 | n-butyl | ethyl | OH | H | phenyl |
| 125 | ethyl | n-butyl | OH | H | phenyl |
| 126 | n-butyl | ethyl | OH | H | 4-fluorophenyl |
| 127 | n-butyl | ethyl | OH | H | 4-fluorophenyl |
| 128 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 129 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 131 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 132 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 133 | ethyl | n-butyl | OH | H | phenyl |
| 134 | ethyl | n-butyl | OH | H | phenyl |
| 135 | ethyl | n-butyl | OH | H | phenyl |
| 136 | ethyl | n-butyl | OH | H | phenyl |
| 137 | n-butyl | ethyl | OH | H | phenyl |
| 138 | n-butyl | ethyl | OH | H | phenyl |
| 139 | n-butyl | ethyl | OH | H | phenyl |
| 140 | | | | | phenyl |
| 141 | | | | | |
| 142 | ethyl | n-butyl | H | OH | H |
| 143 | ethyl | n-butyl | OH | H | 3-methoxyphenyl |
| 144 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 262 | ethyl | n-butyl | OH | H | 3-methoxyphenyl |
| 263 | ethyl | n-butyl | H | OH | H |
| 264 | ethyl | n-butyl | OH | H | 3-trifluoromethylphenyl |
| 265 | ethyl | n-butyl | H | OH | H |
| 266 | ethyl | n-butyl | OH | H | 3-hydroxyphenyl |
| 267 | ethyl | n-butyl | OH | H | 3-hydroxyphenyl |
| 268 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 269 | ethyl | n-butyl | H | OH | H |

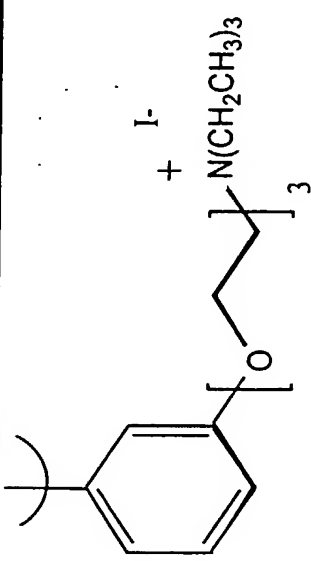
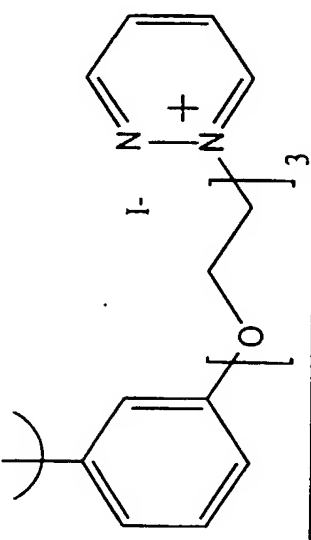
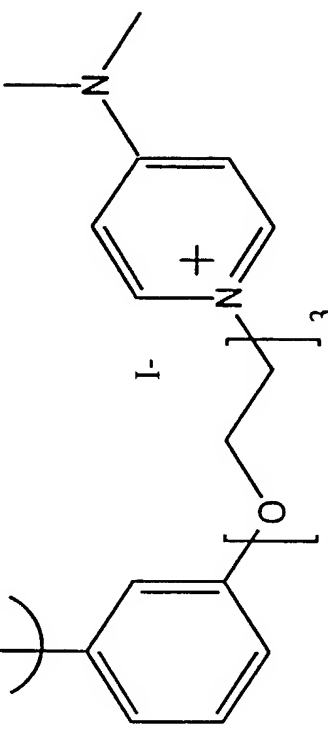
| | | | | | |
|-----|---------|---------|----|----|-----------------|
| 270 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 271 | ethyl | n-butyl | OH | H | 3-methoxyphenyl |
| 272 | ethyl | n-butyl | H | OH | H |
| 273 | ethyl | n-butyl | H | OH | H |
| 274 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 275 | ethyl | n-butyl | H | OH | H |
| 276 | ethyl | n-butyl | OH | H | 3-methoxyphenyl |
| 277 | ethyl | n-butyl | OH | H | 3-fluorophenyl |
| 278 | ethyl | n-butyl | H | OH | 2-fluorophenyl |
| 279 | ethyl | n-butyl | H | OH | 3-fluorophenyl |
| 280 | ethyl | n-butyl | OH | H | 2-fluorophenyl |
| 281 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 282 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 283 | ethyl | n-butyl | H | OH | H |
| 284 | ethyl | n-butyl | OH | H | 4-fluorophenyl |
| 286 | ethyl | ethyl | OH | H | phenyl |
| 287 | ethyl | ethyl | OH | H | phenyl |
| 288 | methyl | methyl | OH | H | phenyl |
| 289 | n-butyl | n-butyl | OH | H | phenyl |
| 290 | n-butyl | n-butyl | OH | H | phenyl |
| 291 | n-butyl | n-butyl | OH | H | phenyl |
| 292 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 293 | n-butyl | n-butyl | OH | H | phenyl |
| 294 | n-butyl | n-butyl | OH | H | phenyl |

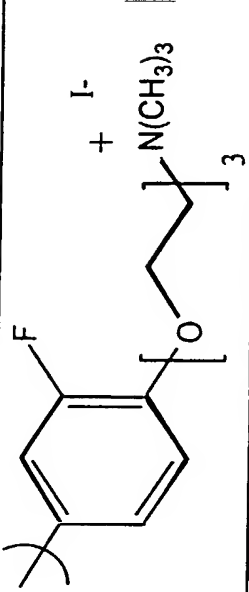
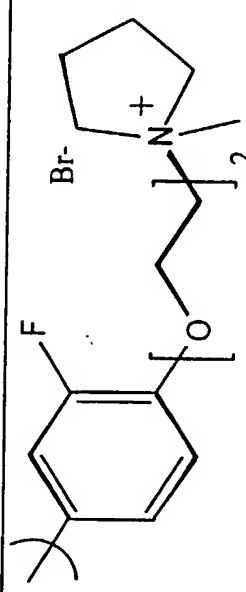
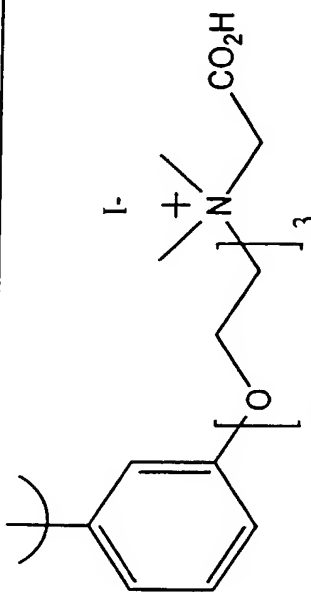
020000

| | | | | | |
|------|-------|---------|----|---|--|
| 295 | ethyl | n-butyl | OH | H |  |
| 296 | ethyl | n-butyl | OH | H |  |
| 1000 | ethyl | n-butyl | OH | H |  |

10068297.020802

| | | | | | |
|------|---------|---------|----|---|---|
| I004 | ethyl | n-butyl | OH | H | $\text{CF}_3\text{COO}-$ $+$ $(\text{CH}_3\text{CH}_2)_3\text{N}$ $\text{NH}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$  |
| I005 | n-butyl | n-butyl | OH | H | $\text{CF}_3\text{COO}-$ $+$ $(\text{CH}_3\text{CH}_2)_3\text{N}$ $\text{NH}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$  |
| I006 | n-butyl | n-butyl | OH | H |  $\text{Br}-$ |

| | | | | | |
|------|---------|---------|----|---|--|
| I007 | n-butyl | n-butyl | OH | H |  |
| I008 | n-butyl | n-butyl | OH | H |  |
| I009 | n-butyl | n-butyl | OH | H |  |
| I010 | n-butyl | n-butyl | OH | H | 3-fluoro-4-methoxyphenyl |

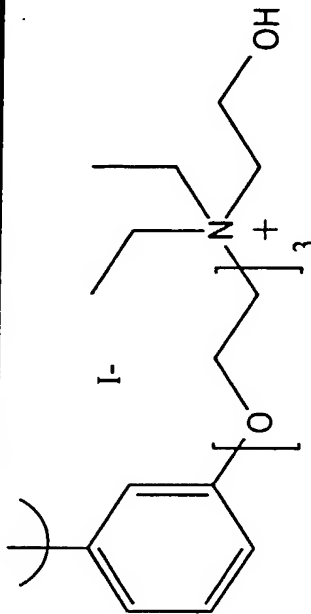
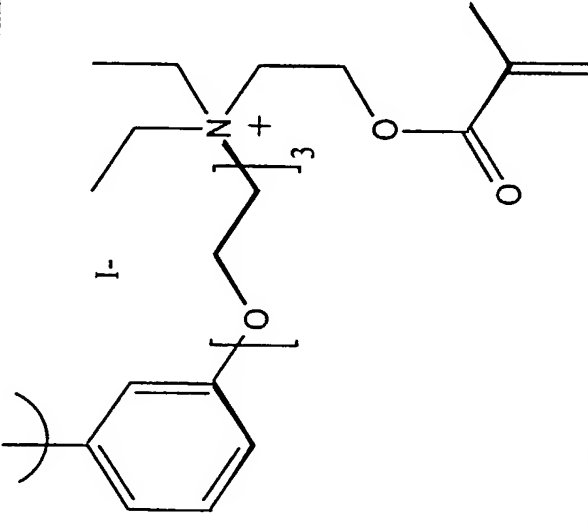
| | | | | | | |
|------|---------|---------|---------|----|---|--|
| I011 | n-butyl | n-butyl | n-butyl | OH | H | 3-fluoro-4-(5-triethylammoniumpentyloxy)phenyl, trifluoroacetate salt |
| I012 | n-butyl | n-butyl | n-butyl | OH | H | 4-hydroxyphenyl |
| I013 | n-butyl | n-butyl | n-butyl | OH | H |  |
| I014 | n-butyl | n-butyl | n-butyl | OH | H | 4-methoxyphenyl |
| I015 | n-butyl | n-butyl | n-butyl | OH | H |  |
| I016 | n-butyl | n-butyl | n-butyl | OH | H |  |

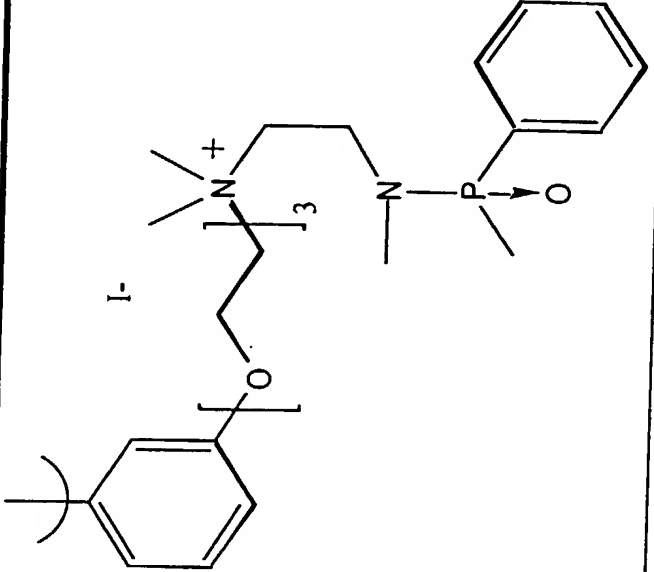
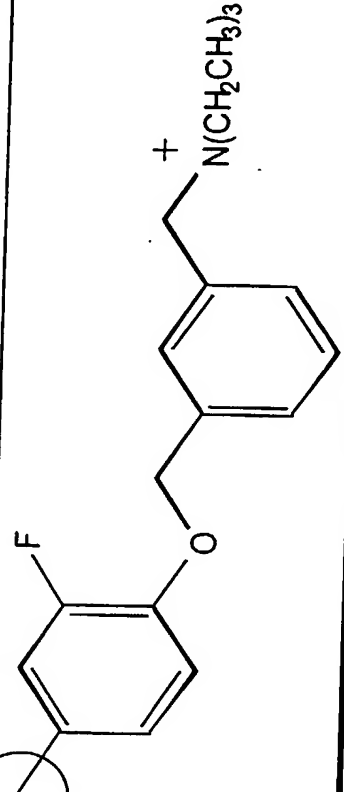
10056297-020302

10068297, 0208001

| | | | | | |
|------|---------|---------|----|---|--|
| 1017 | n-butyl | n-butyl | OH | H | |
| 1018 | n-butyl | n-butyl | OH | H | |

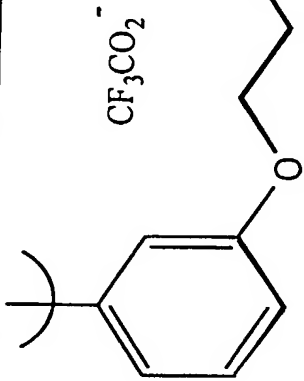
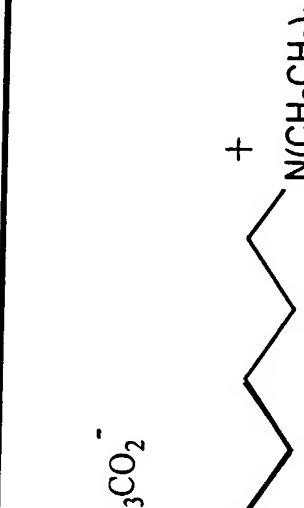
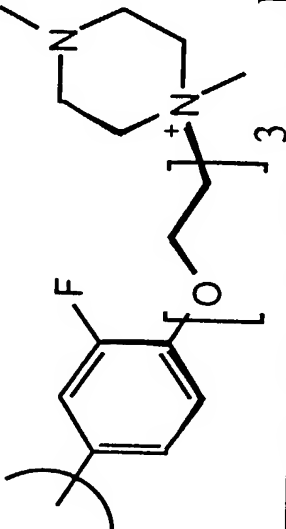
| | | | | | |
|------|---------|---------|----|---|--|
| 1019 | n-butyl | n-butyl | OH | H | |
| 1020 | n-butyl | n-butyl | OH | H | |
| 1021 | n-butyl | n-butyl | OH | H | |

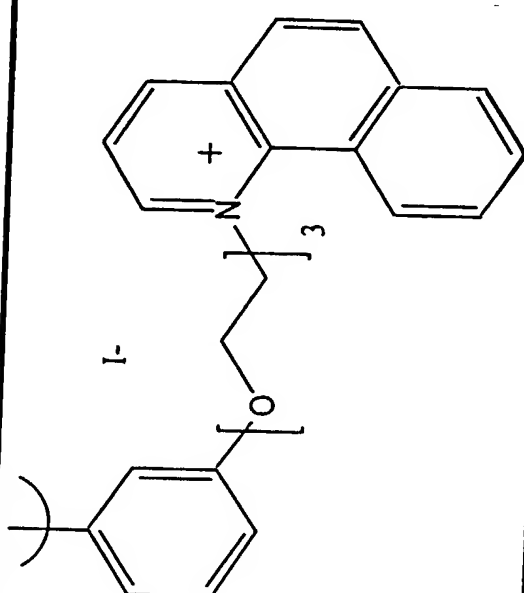
| | | | | | |
|------|---------|---------|----|---|---|
| I022 | n-butyl | n-butyl | OH | H |  |
| I023 | n-butyl | n-butyl | OH | H |  |

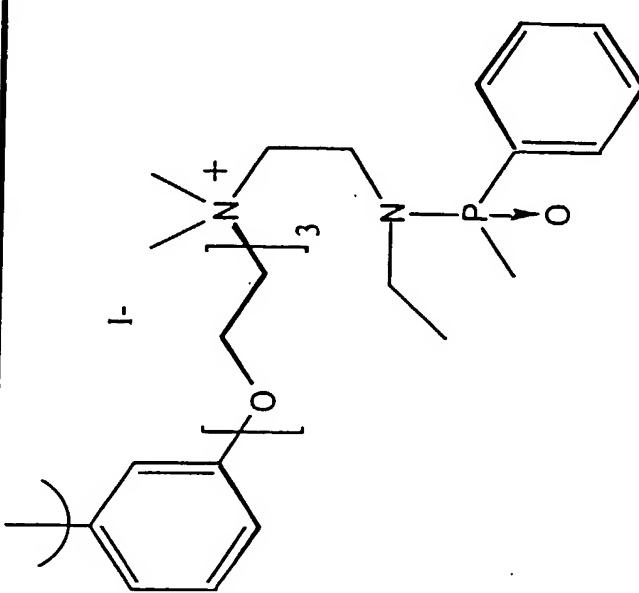
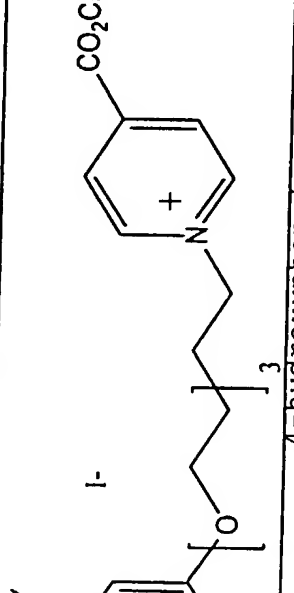
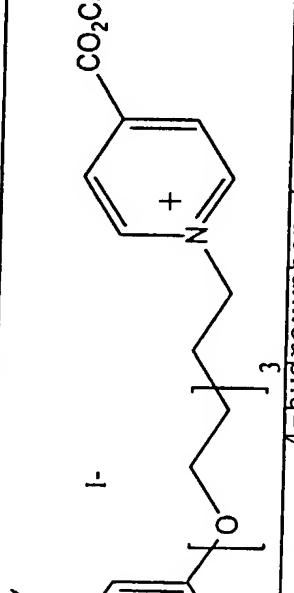
| | | | | | |
|------|---------|---------|----|---|--|
| 1024 | n-butyl | n-butyl | OH | H |  |
| 1025 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|--|
| 1026 | n-butyl | n-butyl | OH | H | |
| 1027 | n-butyl | n-butyl | OH | H | |
| 1028 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1029 | n-butyl | n-butyl | OH | H | |
| 1030 | n-butyl | n-butyl | OH | H | |
| 1031 | n-butyl | n-butyl | OH | H | |

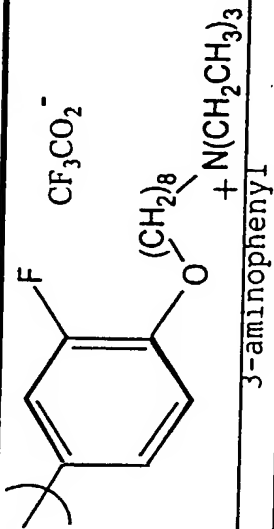
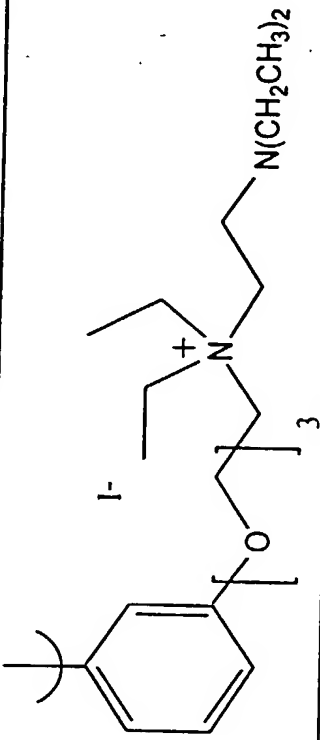
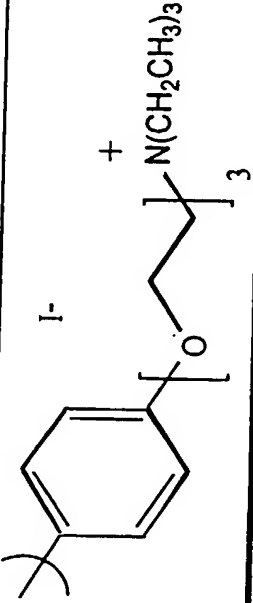
| | | | | | |
|------|---------|---------|----|---|--|
| 1032 | n-butyl | n-butyl | OH | H |  CF_3CO_2^-  $\text{N}(\text{CH}_2\text{CH}_3)_3^+$ Br^- |
| 1033 | n-butyl | n-butyl | OH | H |  $\text{N}(\text{CH}_2\text{CH}_3)_3^+$ Br^- |

| | | | | | |
|------|---------|---------|----|---|--|
| 1034 | n-butyl | n-butyl | OH | H |  |
|------|---------|---------|----|---|--|

| | | | | | |
|------|---------|---------|----|---|--|
| I035 | n-butyl | n-butyl | OH | H |  |
| I036 | n-butyl | n-butyl | OH | H |  |
| I037 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|---|
| 1038 | n-butyl | n-butyl | OH | H | <p>I- phenyl</p> |
| 1039 | n-butyl | n-butyl | OH | H | <p>CF₃CO₂⁻</p> |
| 1040 | n-butyl | n-butyl | OH | H | |
| 1041 | n-butyl | n-butyl | OH | H | <p>I-</p> |

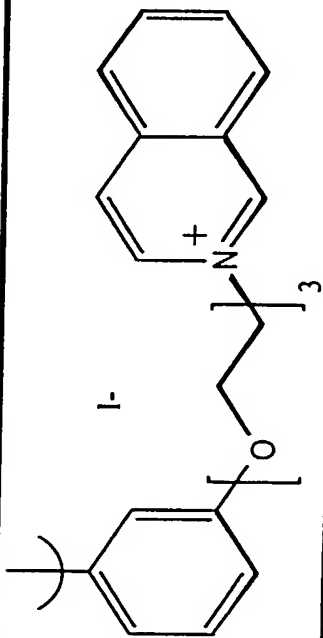
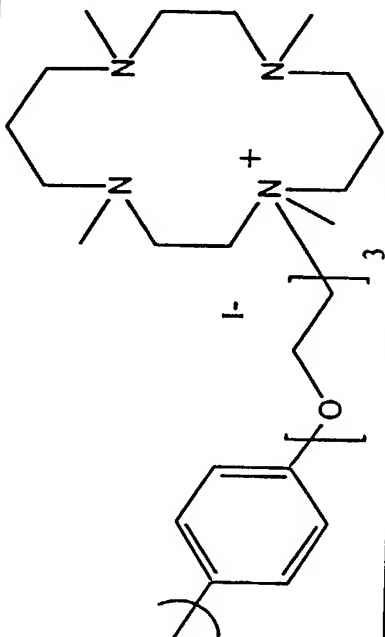
| | | | | | |
|------|---------|---------|----|---|--|
| I042 | n-butyl | n-butyl | OH | H | |
| I043 | n-butyl | n-butyl | OH | H | |
| I044 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1045 | n-butyl | n-butyl | OH | H |  CF_3CO_2^- $(\text{CH}_2)_8\text{O}$ $+ \text{N}(\text{CH}_2\text{CH}_3)_3$ 3-aminophenyl |
| 1046 | n-butyl | n-butyl | OH | H | |
| 1047 | n-butyl | n-butyl | OH | H |  I^- $\text{N}(\text{CH}_2\text{CH}_3)_2$ $\text{N}(\text{CH}_2\text{CH}_3)_3$ |
| 1048 | n-butyl | n-butyl | OH | H |  I^- $\text{N}(\text{CH}_2\text{CH}_3)_3$ |

102

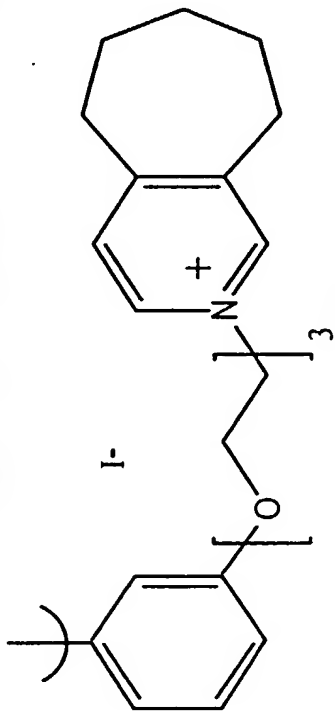
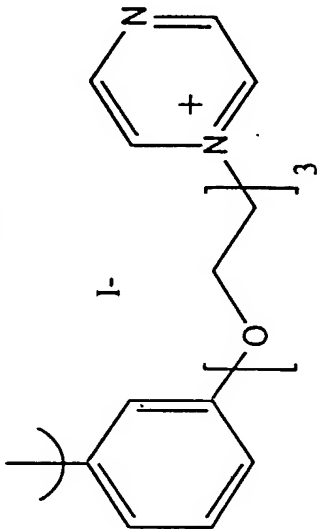
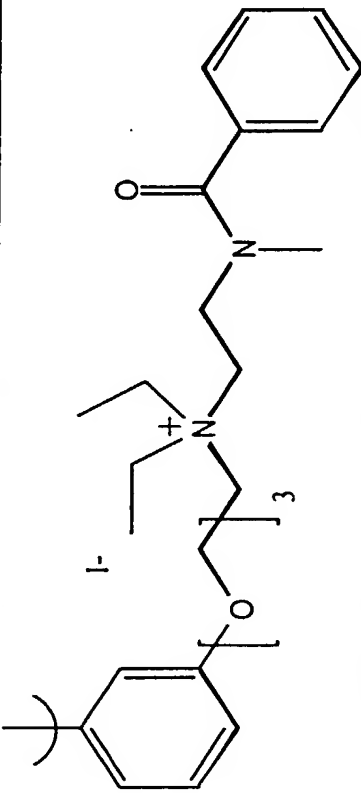
| | | | | | |
|------|---------|---------|----|---|--|
| 1049 | n-butyl | n-butyl | OH | H | |
| 1050 | n-butyl | n-butyl | OH | H | |
| 1051 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1052 | n-butyl | n-butyl | OH | H | |
| 1053 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|---|
| 1054 | n-butyl | n-butyl | OH | H |  |
| 1055 | n-butyl | n-butyl | OH | H |  |

SRL 6071
(C-3021/2)

105

| | | | | | |
|------|---------|---------|----|---|--|
| I056 | n-butyl | n-butyl | OH | H |  <p>Chemical structure of a polyether polymer. The main chain consists of a phenyl ring connected to an ether linkage, which is then connected to a quaternary pyridinium salt side chain. The side chain is represented as I^- and the pyridinium ring is shown with a positive charge.</p> |
| I057 | n-butyl | n-butyl | OH | H |  <p>Chemical structure of a polyether polymer. The main chain consists of a phenyl ring connected to an ether linkage, which is then connected to a quaternary pyridinium salt side chain. The side chain is represented as I^- and the pyridinium ring is shown with a positive charge.</p> |
| I058 | n-butyl | n-butyl | OH | H |  <p>Chemical structure of a polyether polymer. The main chain consists of a phenyl ring connected to an ether linkage, which is then connected to a quaternary pyridinium salt side chain. The side chain is represented as I^- and the pyridinium ring is shown with a positive charge.</p> |

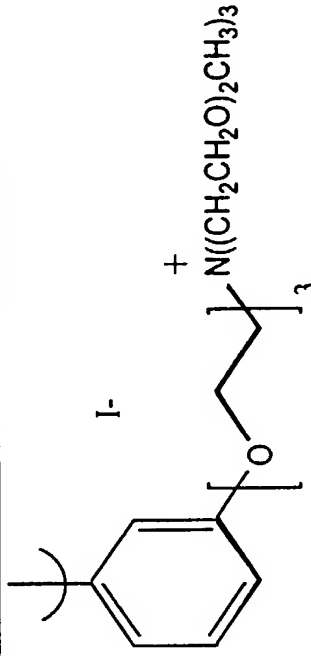
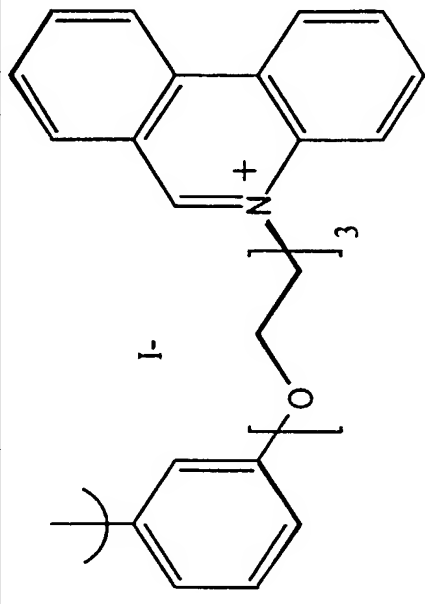
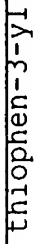
10068297.020802

11

106

| | | | | | |
|------|---------|---------|----|---|--|
| 1059 | n-butyl | n-butyl | OH | H | |
| 1060 | ethyl | n-butyl | OH | H | |
| 1061 | n-butyl | n-butyl | OH | H | |
| 1062 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1063 | n-butyl | n-butyl | OH | H | |
| 1064 | n-butyl | n-butyl | OH | H | |

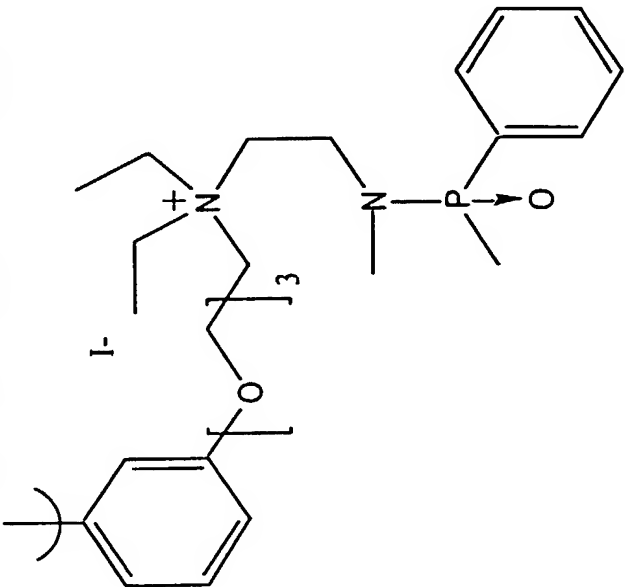
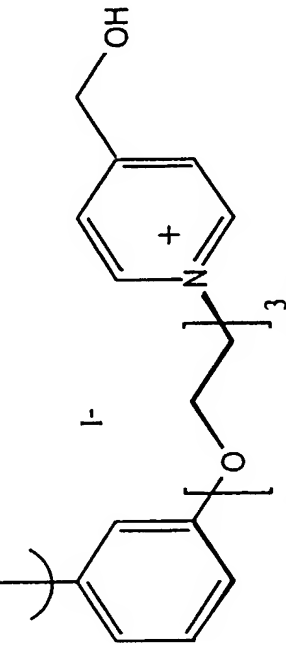
| | | | | | |
|------|---------|---------|----|---|---|
| I065 | n-butyl | n-butyl | OH | H |  |
| I066 | n-butyl | n-butyl | OH | H |  |
| I067 | n-butyl | n-butyl | OH | H |  |

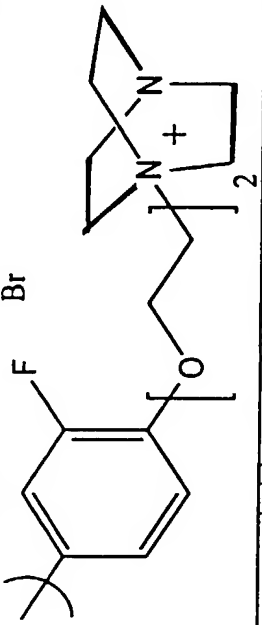
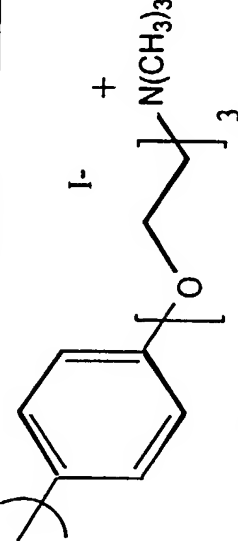
SRL 6071
(C-3021/2)

109

| | | | | | |
|------|---------|---------|----|---|--------|
| 1068 | n-butyl | n-butyl | OH | H | |
| 1069 | n-butyl | n-butyl | OH | H | phenyl |
| 1070 | n-butyl | n-butyl | OH | H | |

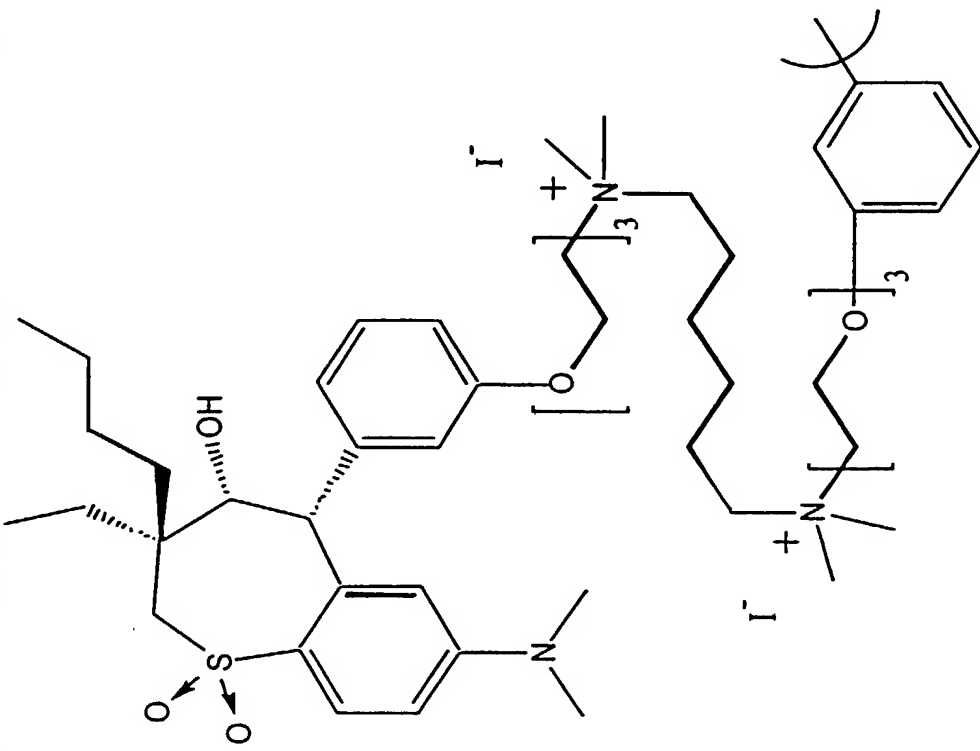
10068297.020802

| | | | | | |
|------|---------|---------|----|---|--|
| 1071 | n-butyl | n-butyl | OH | H |  <p>The structure shows a polymer chain with a p-phenylene backbone. One end of the chain is terminated with a polyether group: $-(CH_2)_3-O-$. The other end is terminated with a phosphonium salt group: $-(CH_2)_3-N^+(CH_2CH_3)_3-P(=O)(CH_3)_2-C_6H_5$. A counterion I^- is shown.</p> |
| 1072 | n-butyl | n-butyl | OH | H |  <p>The structure shows a polymer chain with a p-phenylene backbone. One end of the chain is terminated with a polyether group: $-(CH_2)_3-O-$. The other end is terminated with a pyridinium salt group: $-(CH_2)_3-N^+(C_5H_4CH_2OH)$. A counterion I^- is shown.</p> |

| | | | | | |
|------|---------|---------|----|---|--|
| 1073 | n-butyl | n-butyl | OH | H |  |
| 1074 | ethyl | n-butyl | OH | H | 3-fluoro-4-methoxyphenyl |
| 1075 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 1076 | n-butyl | n-butyl | OH | H | |
| 1077 | n-butyl | n-butyl | OH | H |  |
| 1078 | ethyl | n-butyl | OH | H | 3-hydroxyphenyl |
| | | | | | 4-hydroxyphenyl |

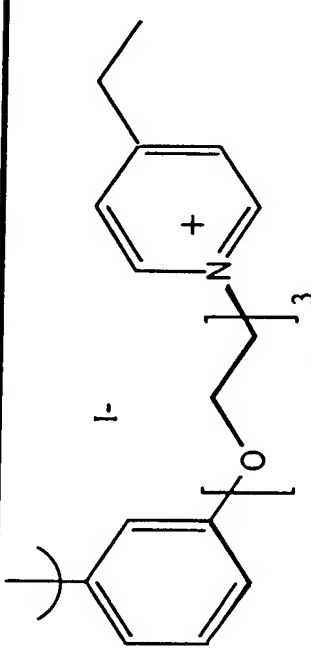
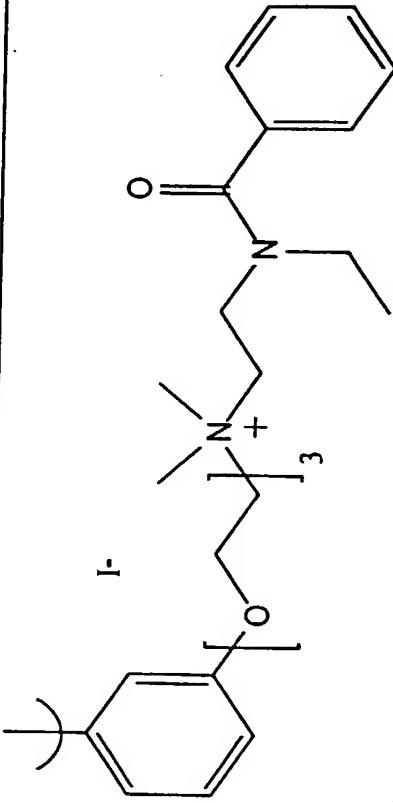
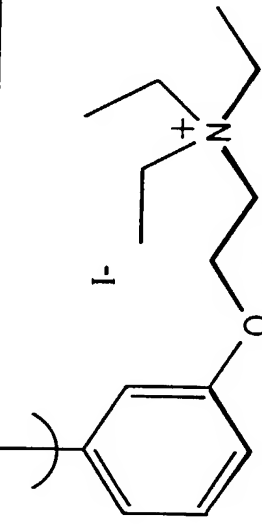
SRL 6071
(C-3021/2)

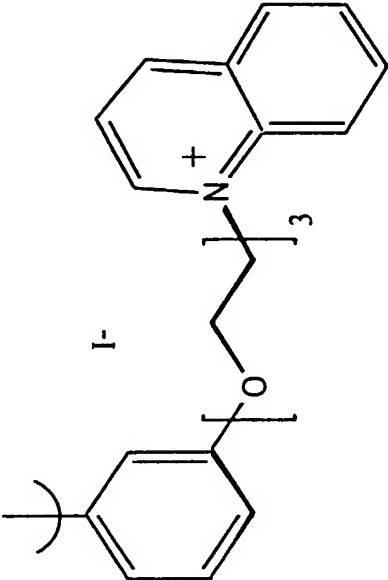
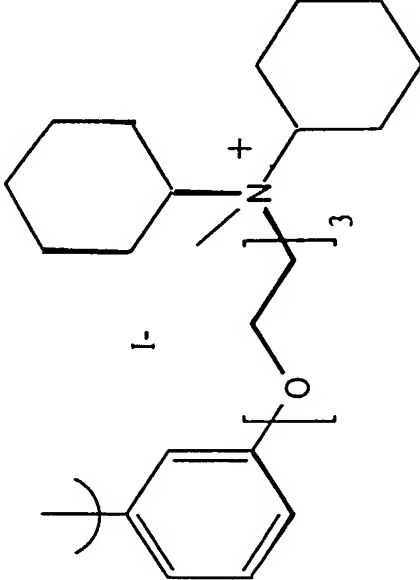
112

| | | | | | |
|------|-------|---------|----|---|---|
| I079 | ethyl | n-butyl | OH | H |  |
|------|-------|---------|----|---|---|

30068297.020802

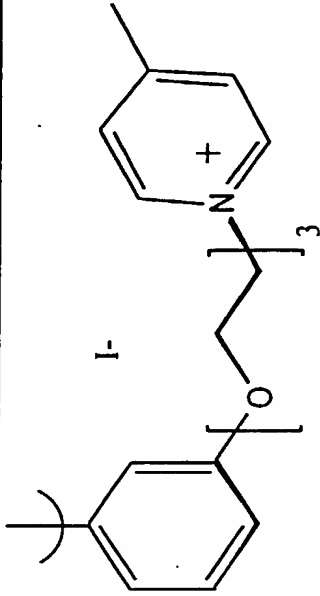
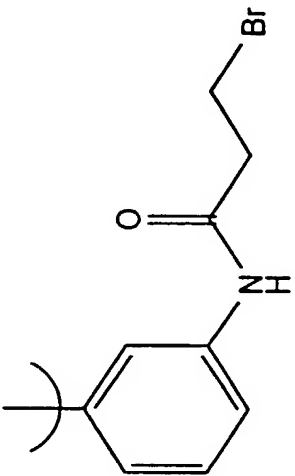
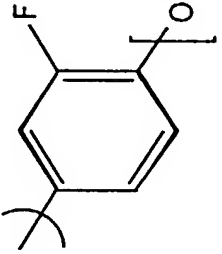
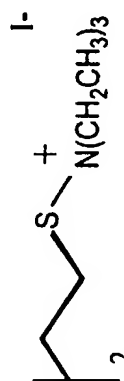
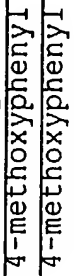
| | | | | | |
|------|---------|---------|----|---|--|
| 1080 | n-butyl | n-butyl | OH | H | |
| 1081 | n-butyl | n-butyl | OH | H | |
| 1082 | n-butyl | n-butyl | OH | H | |
| 1083 | n-butyl | n-butyl | OH | H | |

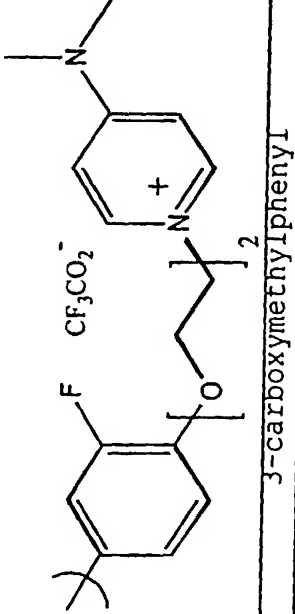
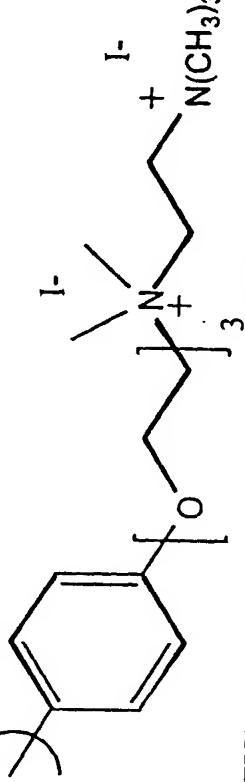
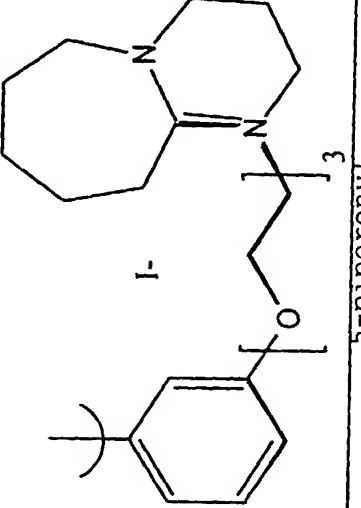
| | | | | | |
|------|---------|---------|----|---|--|
| 1084 | n-butyl | n-butyl | OH | H |  |
| 1085 | n-butyl | n-butyl | OH | H | thiophen-3-yl |
| 1086 | n-butyl | n-butyl | OH | H |  |
| 1087 | n-butyl | n-butyl | OH | H |  |

| | | | | | | | 3,4-methylenedioxyphenyl | |
|------|---------|---------|----|---|--|--|---|--|
| | | | | | | | 4-methoxyphenyl | |
| | | | | | | | | |
| I088 | ethyl | n-butyl | OH | H | | |  | |
| I089 | ethyl | n-butyl | OH | H | | | | |
| I090 | n-butyl | n-butyl | OH | H | | | | |
| I091 | n-butyl | n-butyl | OH | H | | |  | |

| | | | | | |
|------|---------|---------|----|---|--|
| I092 | n-butyl | n-butyl | OH | H | |
| I093 | n-butyl | n-butyl | OH | H | |

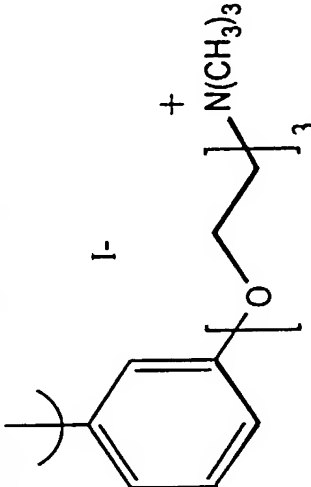
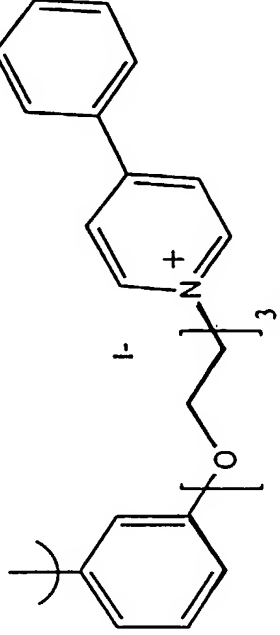
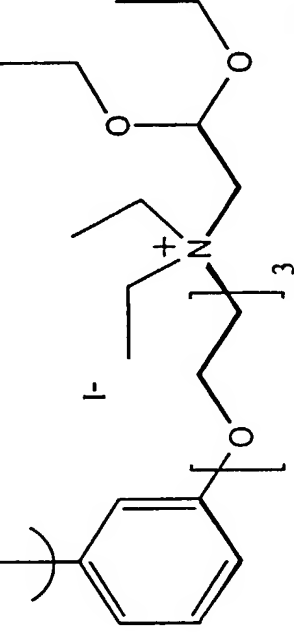
| | | | | | |
|------|---------|---------|----|---|--|
| 1094 | n-butyl | n-butyl | OH | H | |
| 1095 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1096 | n-butyl | n-butyl | OH | H |  |
| 1097 | n-butyl | n-butyl | OH | H |  |
| 1098 | n-butyl | n-butyl | OH | H |  |
| 1099 | ethyl | n-butyl | OH | H |  |
| 1100 | n-butyl | n-butyl | OH | H |  |

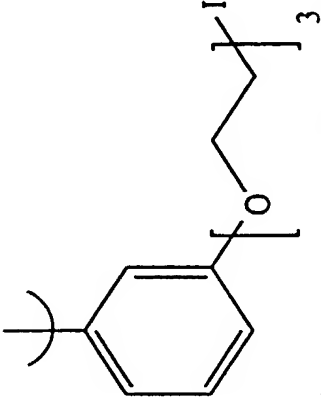
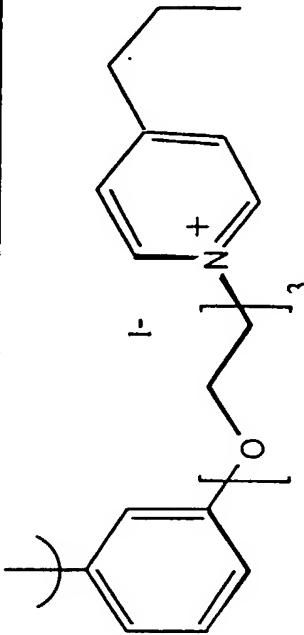
| | | | | | |
|------|---------|---------|----|---|---|
| 1101 | n-butyl | n-butyl | OH | H |  <p>3-carboxymethylphenyl</p> |
| 1102 | n-butyl | n-butyl | OH | H | |
| 1103 | n-butyl | n-butyl | OH | H |  <p>I-</p> |
| 1104 | n-butyl | n-butyl | OH | H |  <p>I-</p> <p>5-piperonyl</p> <p>3-hydroxyphenyl</p> |
| 1105 | n-butyl | n-butyl | OH | H | |
| 1106 | n-butyl | n-butyl | OH | H | |

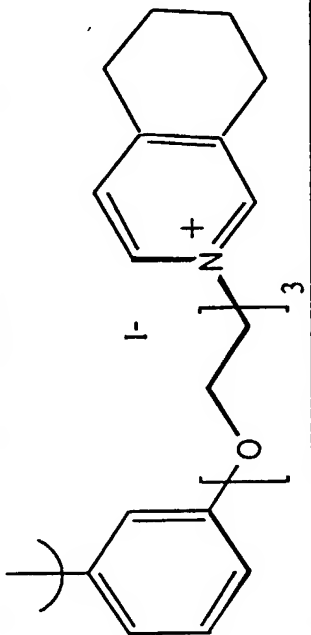
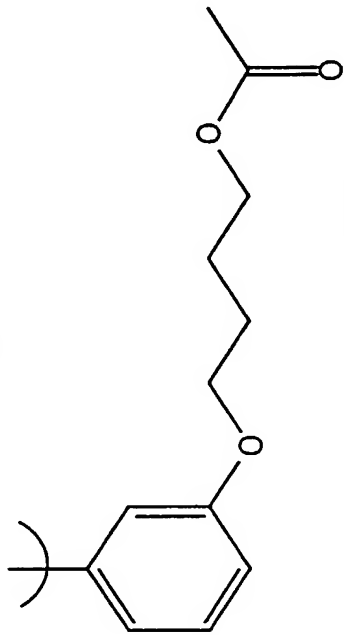
| | | | | | |
|------|---------|---------|----|---|-----------|
| 1107 | n-butyl | n-butyl | OH | H | |
| 1108 | n-butyl | n-butyl | OH | H | 3-pyridyl |
| 1109 | n-butyl | n-butyl | OH | H | |
| 1110 | n-butyl | n-butyl | OH | H | |

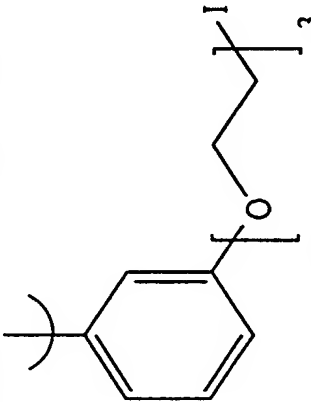
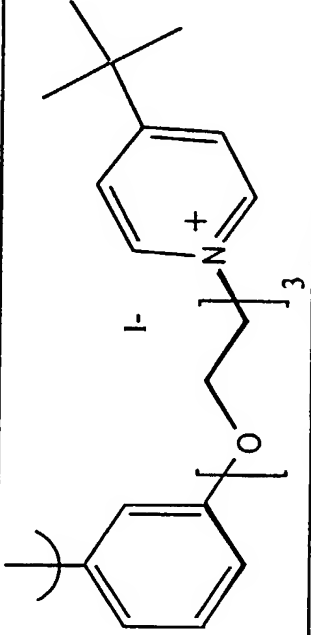
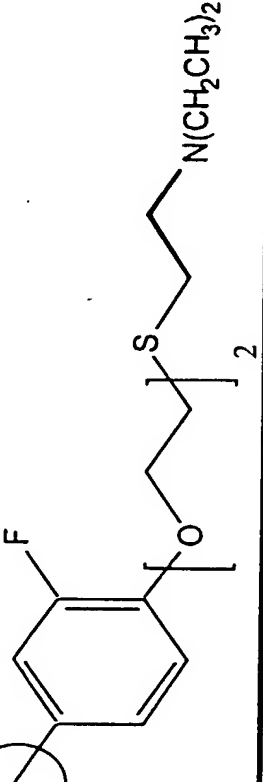
| | | | | | |
|------|---------|---------|----|---|-----------------|
| III1 | n-butyl | n-butyl | OH | H | |
| III2 | n-butyl | n-butyl | OH | H | 4-pyridyl |
| III3 | n-butyl | n-butyl | OH | H | |
| III4 | n-butyl | n-butyl | OH | H | 3-methoxyphenyl |
| III5 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| III6 | ethyl | n-butyl | OH | H | 3-tolyl |

| | | | | | |
|-------|---------|---------|----|---|--|
| III7 | ethyl | n-butyl | OH | H |  |
| III8 | ethyl | n-butyl | OH | H | 3-fluoro-4-hydroxyphenyl |
| III9 | n-butyl | n-butyl | OH | H |  |
| III20 | n-butyl | n-butyl | OH | H |  |

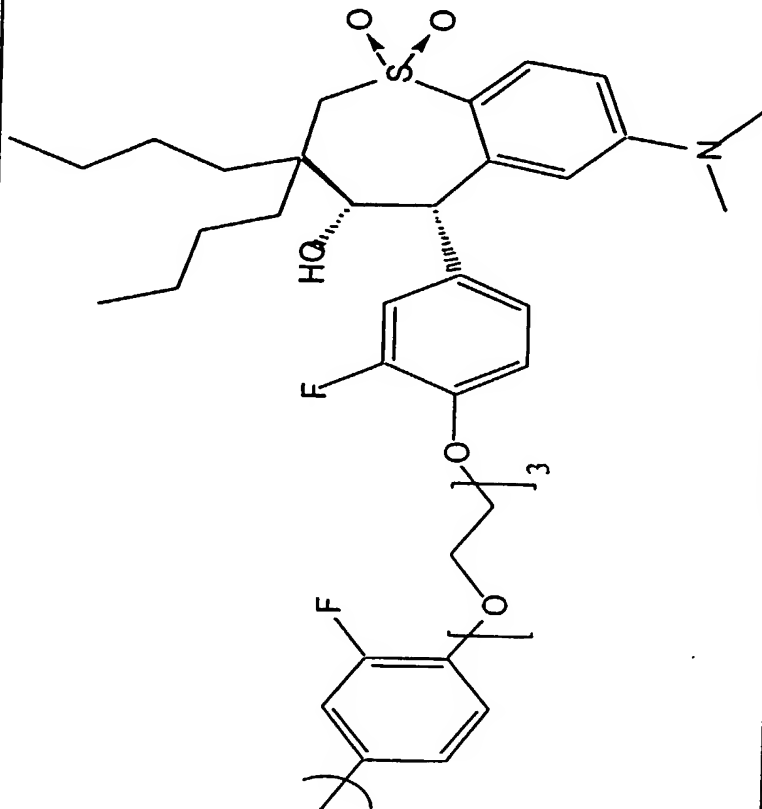
| | | | | | |
|------|---------|---------|----|---|--------------------------|
| 1121 | n-butyl | n-butyl | OH | H | |
| 1122 | n-butyl | n-butyl | OH | H | |
| 1123 | n-butyl | n-butyl | OH | H | phenyl |
| 1124 | n-butyl | n-butyl | OH | H | 3-methoxyphenyl |
| 1125 | n-butyl | n-butyl | OH | H | 3-chloro-4-methoxyphenyl |

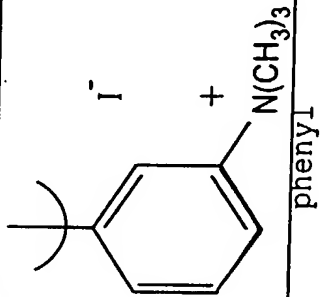
| | | | | | |
|------|---------|---------|----|---|--|
| 1126 | ethyl | n-butyl | OH | H |  |
| 1127 | n-butyl | n-butyl | OH | H |  |
| 1128 | n-butyl | n-butyl | OH | H | 3-fluoro-4-hydroxyphenyl |
| 1129 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 1130 | n-butyl | n-butyl | OH | H | 3-chloro-4-fluorophenyl |
| 1131 | ethyl | n-butyl | OH | H | 4-methoxyphenyl |

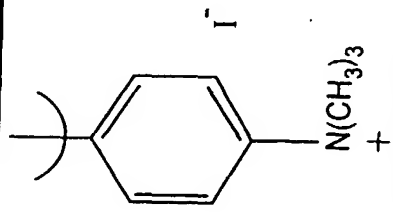
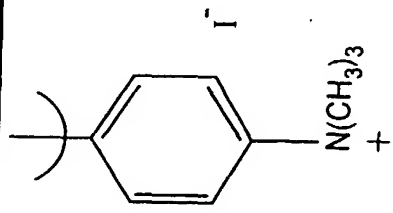
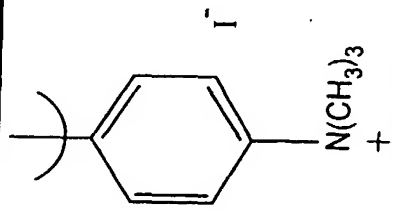
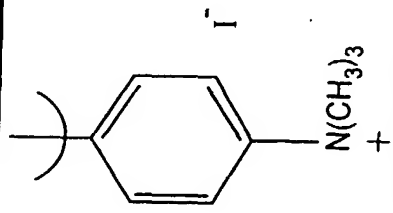
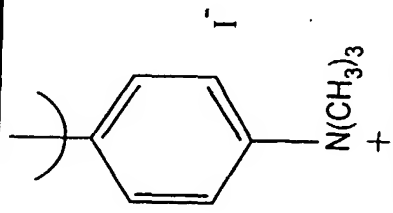
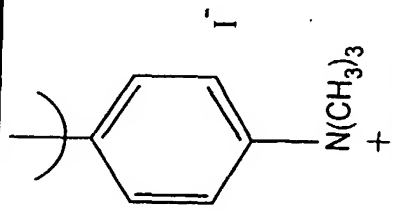
| | | | | | |
|------|---------|---------|----|---|---|
| 1132 | n-butyl | n-butyl | OH | H |  |
| 1133 | n-butyl | n-butyl | OH | H | 4-cyanomethylphenyl |
| 1134 | ethyl | n-butyl | OH | H |  |
| 1135 | n-butyl | n-butyl | OH | H | 3,4-dimethoxyphenyl |

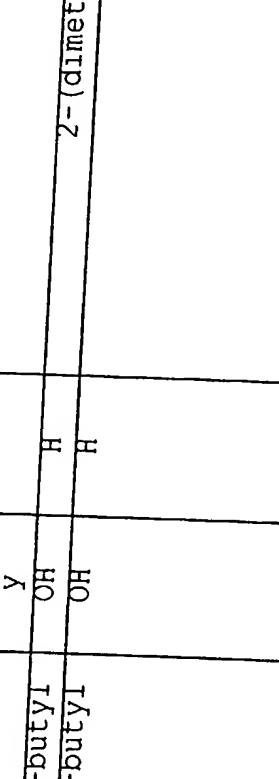
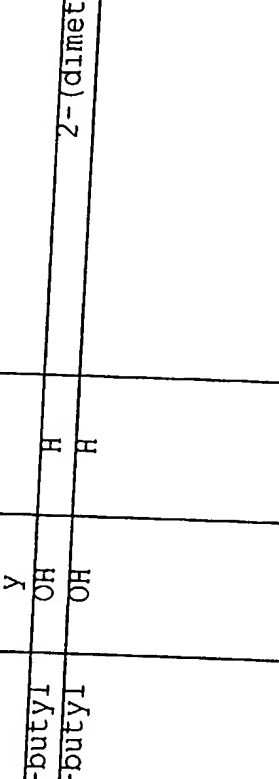
| | | | | | |
|------|---------|---------|----|---|--|
| 1136 | n-butyl | n-butyl | OH | H |  |
| 1137 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 1138 | n-butyl | n-butyl | OH | H |  |
| 1139 | n-butyl | n-butyl | OH | H | 3,4-difluorophenyl |
| 1140 | n-butyl | n-butyl | OH | H | 3-methoxyphenyl |
| 1141 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 1142 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|------------------------------|
| 1190 | n-butyl | n-butyl | OH | H | 2-bromophenyl |
| 1191 | n-butyl | n-butyl | OH | H | 4-(dimethylamino)phenyl |
| 1192 | n-butyl | n-butyl | OH | H | 3-(dimethylamino)phenyl |
| 1193 | n-butyl | n-butyl | OH | H | 4-(2-(2-methylpropyl))phenyl |
| 1194 | n-butyl | n-butyl | OH | H | |
| 1195 | n-butyl | n-butyl | OH | H | 4-methoxyphenyl |

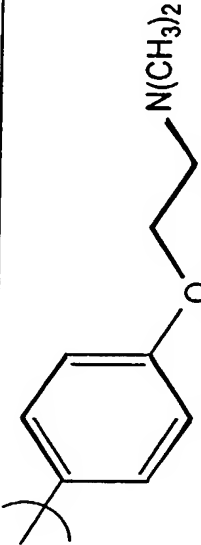
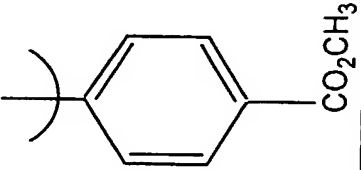


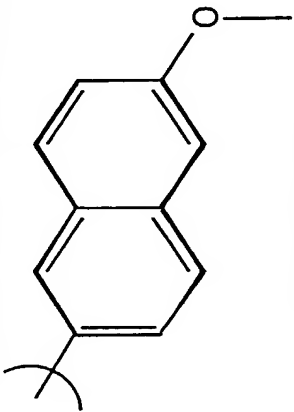
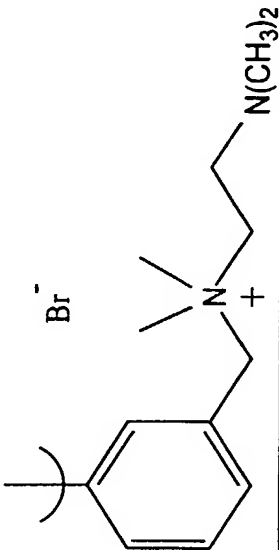
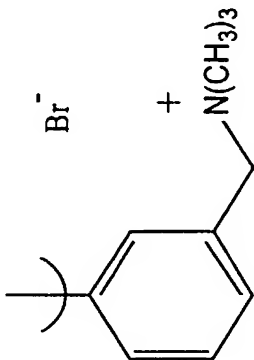
| | | | | | |
|------|---------|---------|---------------------|---------------------|---|
| 1196 | n-butyl | n-butyl | OH | H |  |
| 1197 | n-butyl | ethyl | R3 + R4 = OXO | R3 + R4 = OXO | |
| 1198 | n-butyl | n-butyl | OH | H | |
| | | | | | 4-(pyridinyI-N-oxide) |

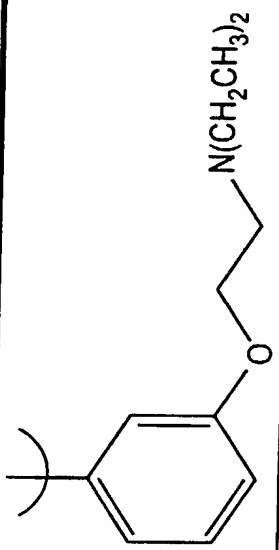
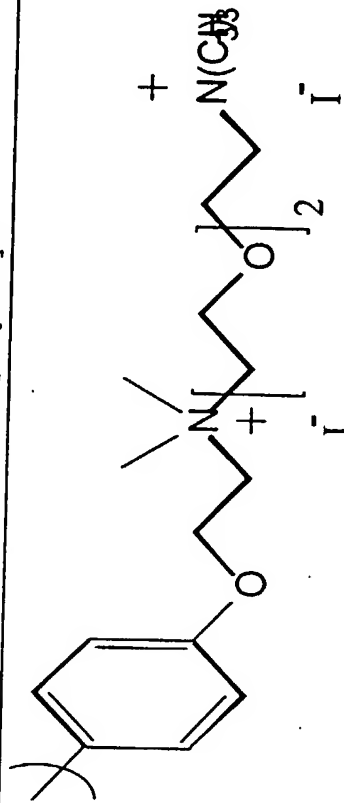
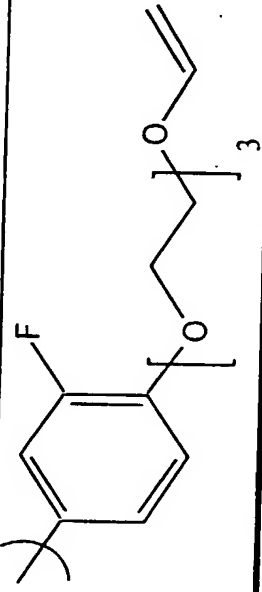
| | | | | | |
|------|---------|---------|----|---|---|
| 1202 | n-butyl | n-butyl | OH | H |  |
| 1203 | n-butyl | n-butyl | OH | H |  |
| 1204 | n-butyl | n-butyl | OH | H |  |
| 1205 | n-butyl | n-butyl | OH | H |  |
| 1206 | n-butyl | n-butyl | OH | H |  |
| 1207 | n-butyl | n-butyl | OH | H |  |

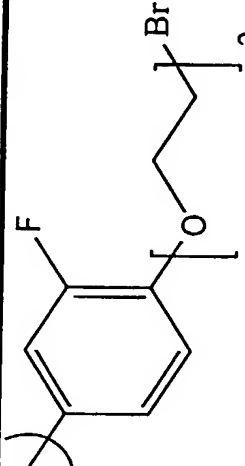
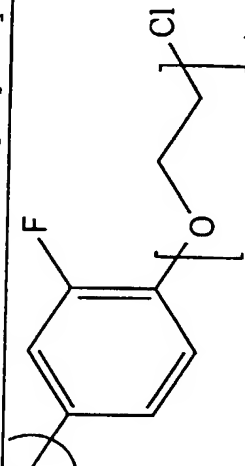
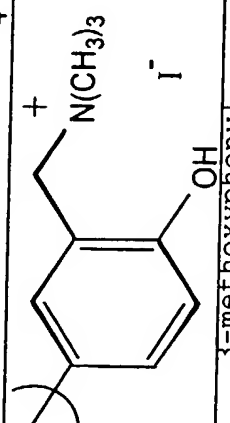
| | | | | | | |
|------|---------|---------|---------|--------|----|--|
| I208 | n-butyl | n-butyl | n-butyl | OH | H |  |
| I209 | n-butyl | n-butyl | n-butyl | acetox | H | |
| I210 | n-butyl | n-butyl | n-butyl | y | H | |
| I211 | ethyl | n-butyl | n-butyl | OH | H | |
| I212 | n-butyl | n-butyl | n-butyl | OH | H |  |
| I213 | n-butyl | n-butyl | ethyl | H | OH | |
| I214 | n-butyl | n-butyl | ethyl | OH | H | |
| I215 | n-butyl | n-butyl | n-butyl | OH | H | |

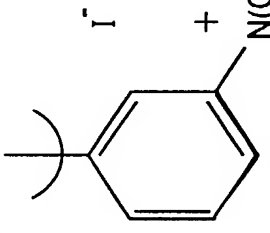
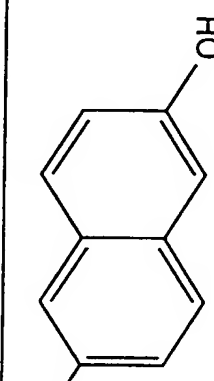
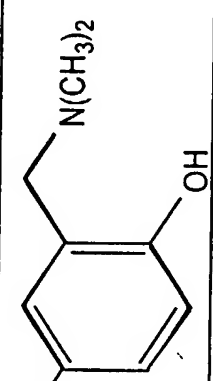
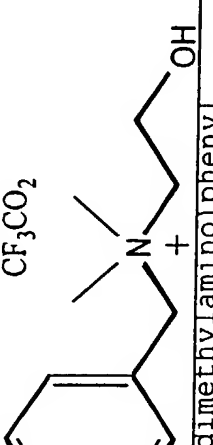
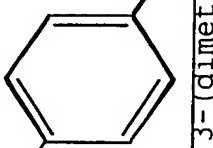
30065997 00000000

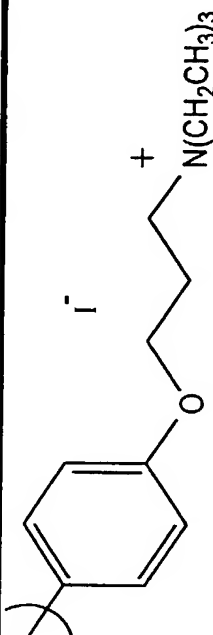
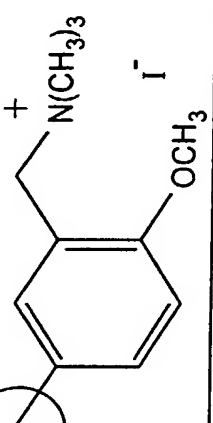
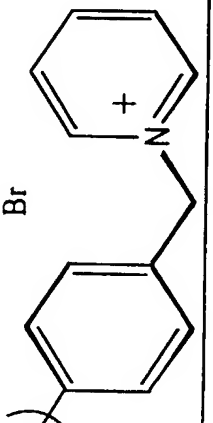
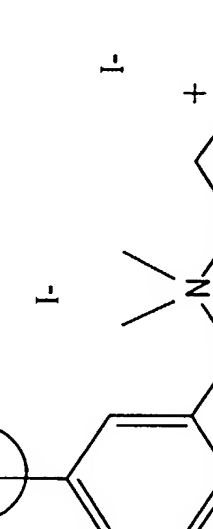
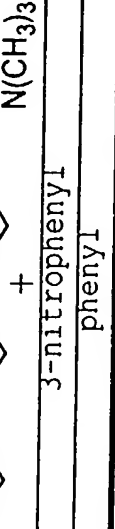

| | | | | | |
|------|---------|---------|----|---|--|
| 1216 | ethyl | n-butyl | OH | H | 5-piperonyl |
| 1217 | n-butyl | n-butyl | OH | H | 4-carboxyphenyl |
| 1218 | n-butyl | n-butyl | OH | H | 4-methoxyphenyl |
| 1219 | n-butyl | n-butyl | OH | H | |
| | | | | |  |
| 1220 | n-butyl | n-butyl | OH | H | 3-methoxyphenyl |
| 1221 | n-butyl | n-butyl | OH | H | |
| | | | | |  |
| 1222 | n-butyl | n-butyl | OH | H | 3-methoxyphenyl |
| 1223 | n-butyl | n-butyl | OH | H | phenyl |
| 1224 | n-butyl | n-butyl | OH | H | 3-nitrophenyl |
| 1225 | n-butyl | ethyl | OH | H | 3-methylphenyl |
| 1226 | ethyl | n-butyl | OH | H | 5-piperonyl |
| 1227 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 1228 | n-butyl | n-butyl | OH | H | 2-pyrrolyl |
| 1229 | n-butyl | n-butyl | OH | H | 3-chloro-4-hydroxyphenyl |
| 1230 | n-butyl | n-butyl | OH | H | phenyl |

| | | | | | |
|------|---------|---------|----|----|--|
| 1231 | n-butyl | n-butyl | OH | H |  |
| 1232 | n-butyl | n-butyl | H | OH | 3-thiophenyl |
| 1233 | n-butyl | n-butyl | OH | H |  |
| 1234 | n-butyl | n-butyl | OH | H |  |

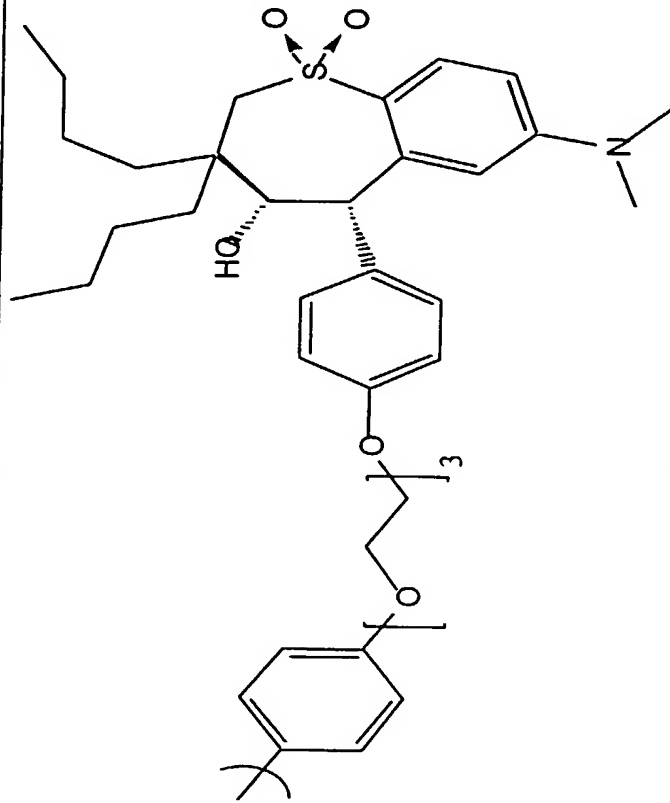
| | | | | | |
|------|---------|---------|----|---|--|
| 1235 | n-butyl | n-butyl | OH | H |  |
| 1236 | n-butyl | n-butyl | OH | H | 4-(bromomethyl)phenyl |
| 1237 | n-butyl | n-butyl | OH | H |  |
| 1238 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|---|
| 1239 | n-butyl | n-butyl | OH | H |  |
| 1240 | n-butyl | n-butyl | OH | H | 4-methoxy-3-methylphenyl |
| 1241 | n-butyl | n-butyl | OH | H | 3-(dimethylaminomethyl)phenyl |
| 1242 | n-butyl | n-butyl | OH | H | |
| 1243 | n-butyl | n-butyl | OH | H |  |
| 1244 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|---|
| 1245 | n-butyl | n-butyl | OH | H |  I^- + $\text{N(CH}_3)_3$ 3-(bromomethyl)phenyl |
| 1246 | n-butyl | n-butyl | OH | H | |
| 1247 | n-butyl | n-butyl | OH | H |  $\text{N(CH}_3)_2$ 3-(dimethylamino)phenyl |
| 1248 | n-butyl | n-butyl | OH | H |  $\text{N(CH}_3)_2$ 3-(dimethylamino)phenyl |
| 1249 | n-butyl | n-butyl | OH | H |  CF_3CO_2^- 3-(dimethylamino)phenyl |
| 1250 | n-butyl | n-butyl | OH | H |  $\text{N(CH}_3)_2$ 1-naphthyl |
| 1251 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| I252 | n-butyl | n-butyl | OH | H |  |
| I253 | n-butyl | n-butyl | OH | H |  |
| I254 | n-butyl | n-butyl | OH | H |  |
| I255 | n-butyl | n-butyl | OH | H |  |
| I256 | n-butyl | n-butyl | OH | H |  |
| I257 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|----|-----------------|
| I258 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| I259 | ethyl | n-butyl | H | OH | H |
| I260 | ethyl | n-butyl | OH | H | 3-hydroxyphenyl |
| I261 | n-butyl | n-butyl | OH | H | |
| I262 | n-butyl | n-butyl | OH | H | |
| I263 | n-butyl | n-butyl | OH | H | |
| I264 | n-butyl | n-butyl | OH | H | |
| I265 | n-butyl | n-butyl | OH | H | |



| | | | | | |
|------|---------|---------|----|---|-------------|
| I266 | n-butyl | n-butyl | OH | H | |
| I267 | n-butyl | ethyl | OH | H | 5-piperonyl |
| I268 | n-butyl | n-butyl | OH | H | |
| I269 | n-butyl | n-butyl | OH | H | |
| I270 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1271 | n-butyl | n-butyl | OH | H | |
| 1272 | n-butyl | n-butyl | OH | H | |

SRL 6071
(C-3021/2)

143

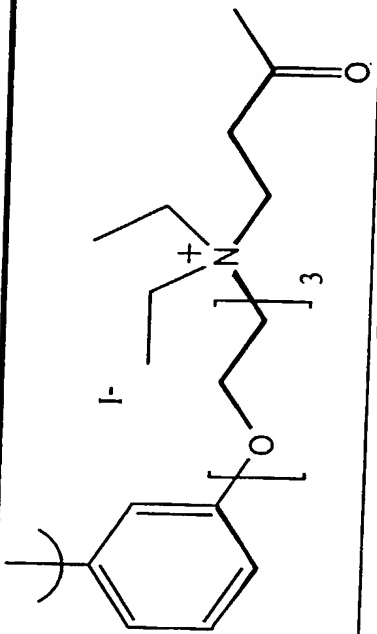
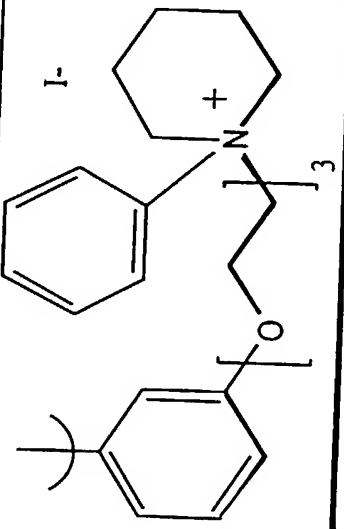
| | | | | | |
|------|---------|---------|----|---|--|
| 1273 | n-butyl | n-butyl | OH | H | |
| 1274 | n-butyl | n-butyl | OH | H | |
| 1275 | n-butyl | n-butyl | OH | H | |

10066297 . 020802

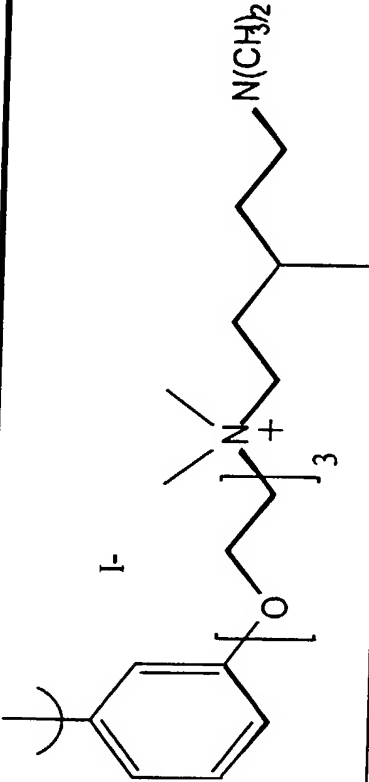
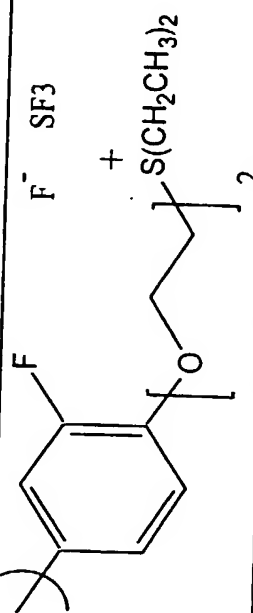
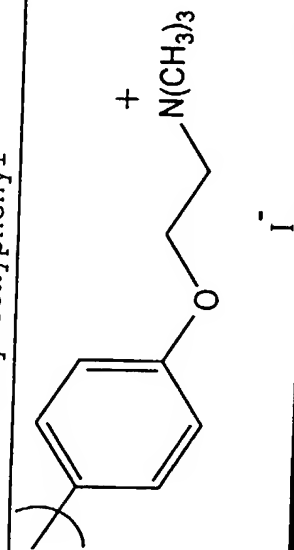
| | | | | | |
|------|---------|---------|----|---|--|
| 1276 | n-butyl | n-butyl | OH | H | |
| 1277 | n-butyl | n-butyl | OH | H | |
| 1278 | n-butyl | n-butyl | OH | H | |

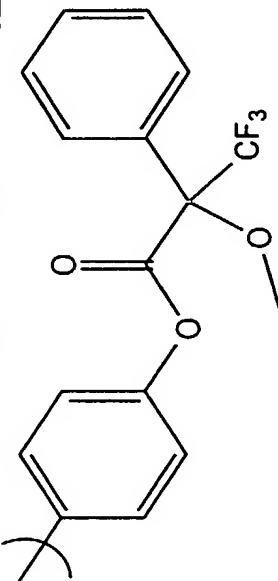
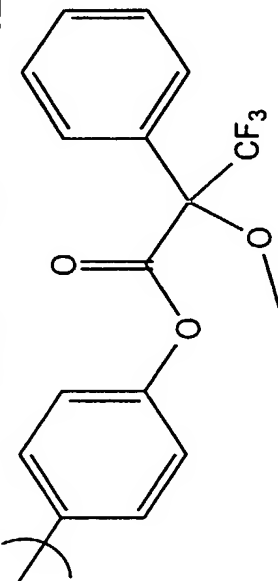
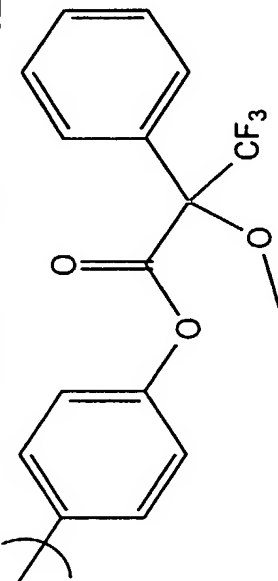
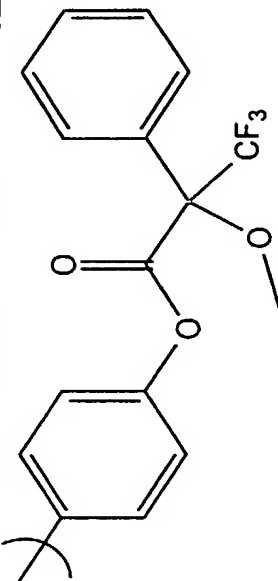
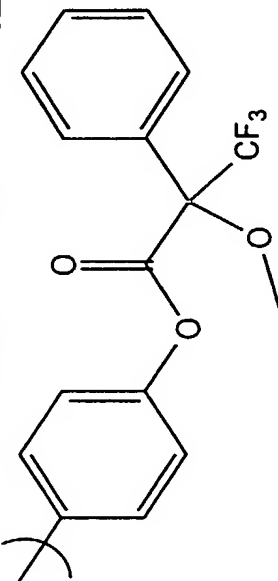
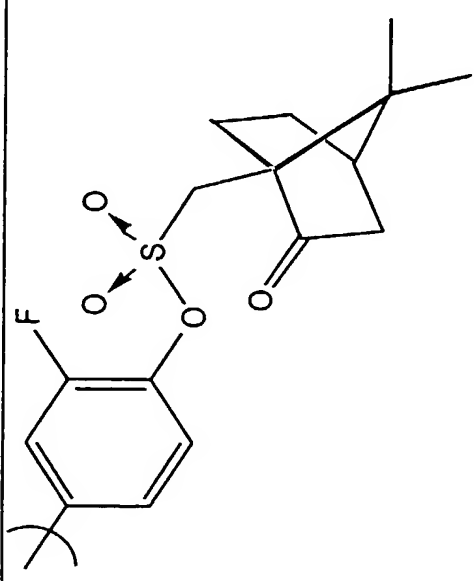
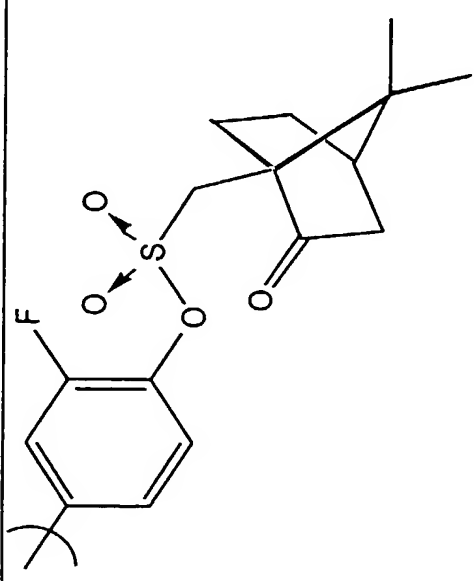
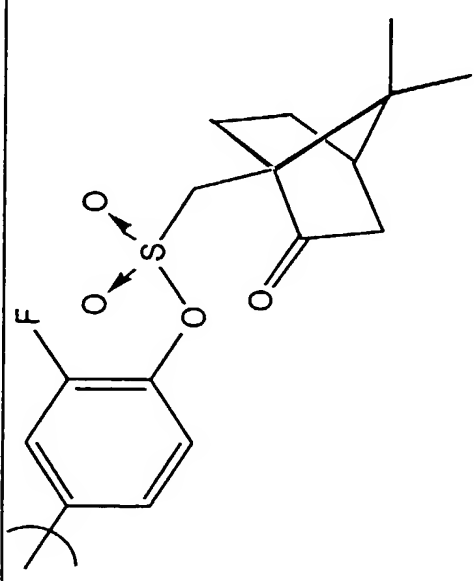
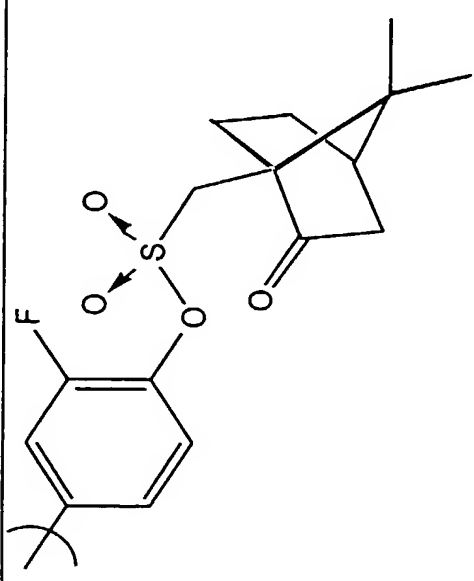
| | | | | | |
|------|---------|---------|----|---|--------------------------|
| 1279 | n-butyl | n-butyl | OH | H | |
| 1280 | n-butyl | n-butyl | OH | H | |
| 1281 | n-butyl | n-butyl | OH | H | |
| 1282 | ethyl | n-butyl | OH | H | 3-fluoro-4-methoxyphenyl |
| 1283 | n-butyl | n-butyl | OH | H | 4-hydroxymethylphenyl |
| 1284 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |
| 1285 | n-butyl | ethyl | OH | H | phenyl |

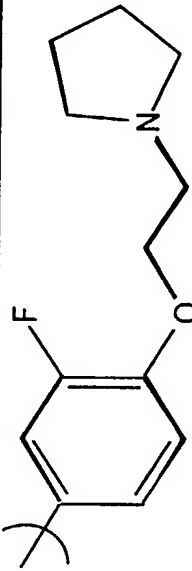
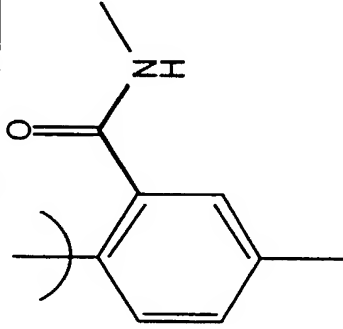
| | | | | | |
|------|---------|---------|----|---|-----------------|
| 1286 | n-butyl | n-butyl | OH | H | |
| 1287 | n-butyl | ethyl | OH | H | 4-hydroxyphenyl |
| 1288 | n-butyl | n-butyl | OH | H | |
| 1289 | n-butyl | n-butyl | OH | H | |

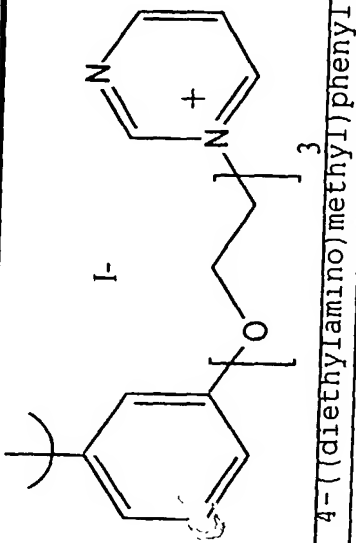
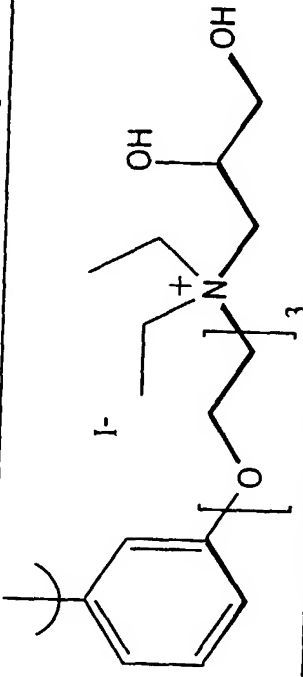
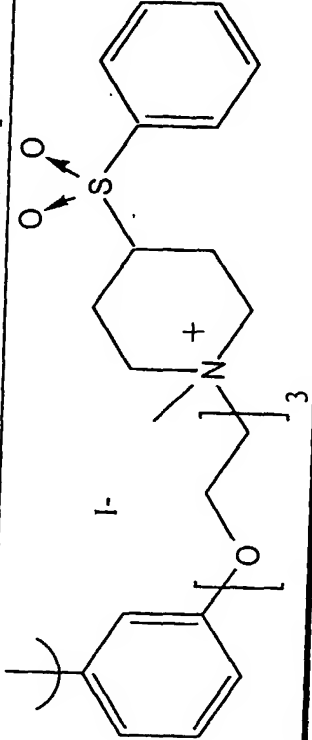
| | | | | | |
|------|---------|---------|----|---|---|
| 1293 | n-butyl | n-butyl | OH | H |  |
| 1294 | n-butyl | n-butyl | OH | H |  |

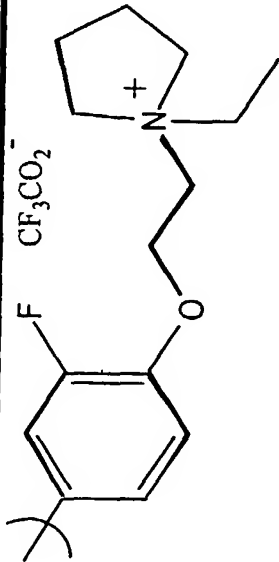
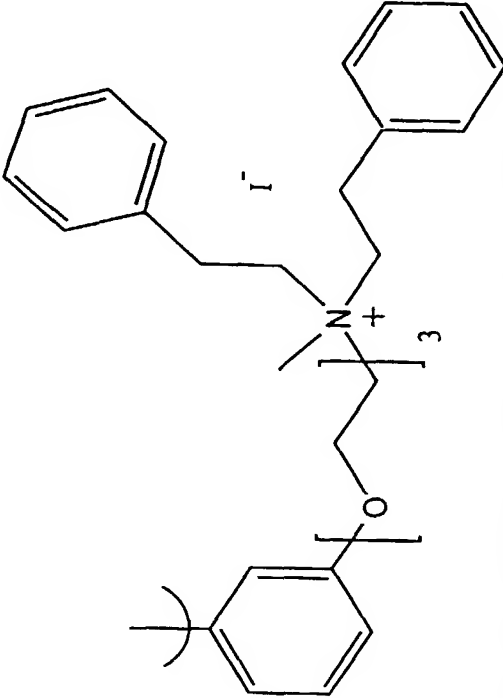
| | | | | | |
|------|---------|---------|----|---|--|
| 1295 | n-butyl | n-butyl | OH | H | |
| 1296 | n-butyl | n-butyl | OH | H | |
| 1297 | n-butyl | n-butyl | OH | H | |

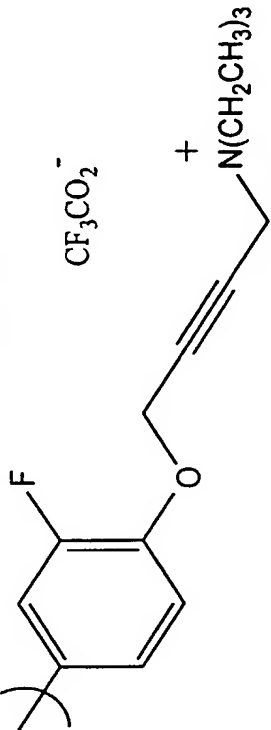
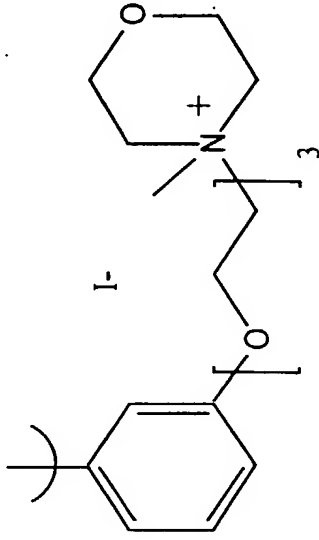
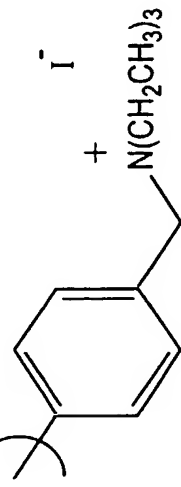
| | | | | | |
|------|---------|---------|----|----|--|
| 1298 | n-butyl | n-butyl | OH | H |  |
| 1299 | n-butyl | n-butyl | OH | H |  |
| 1300 | n-butyl | ethyl | H | OH | |
| 1301 | n-butyl | n-butyl | OH | H | |
| 1302 | n-butyl | n-butyl | OH | H | |
| 1303 | n-butyl | n-butyl | OH | H | |
| | | | | |  |

| | | | | | | |
|------|---------|---------|----|---|-----------------|---|
| 1304 | n-butyl | n-butyl | OH | H | 3-methoxyphenyl |  |
| 1305 | n-butyl | n-butyl | OH | H | 4-fluorophenyl |  |
| 1306 | n-butyl | n-butyl | OH | H | |  |
| 1307 | n-butyl | n-butyl | OH | H | |  |
| 1308 | ethyl | n-butyl | OH | H | |  |
| 1309 | n-butyl | n-butyl | OH | H | 4-methoxyphenyl |  |
| 1310 | ethyl | n-butyl | OH | H | phenyl |  |
| 1311 | n-butyl | ethyl | OH | H | phenyl |  |
| 1312 | n-butyl | ethyl | OH | H | phenyl |  |

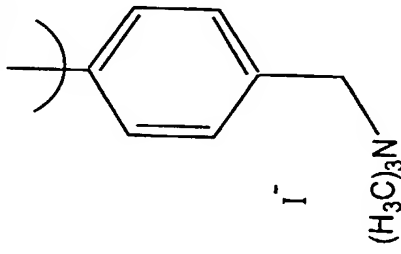
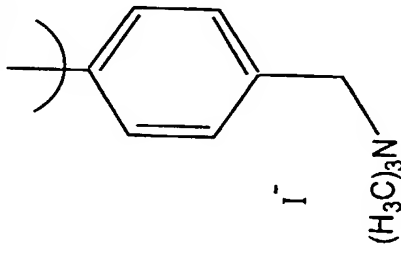
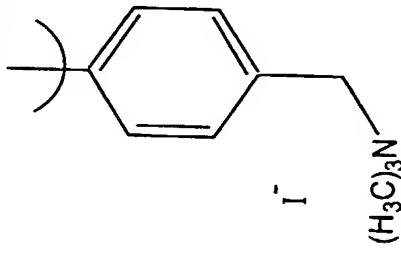
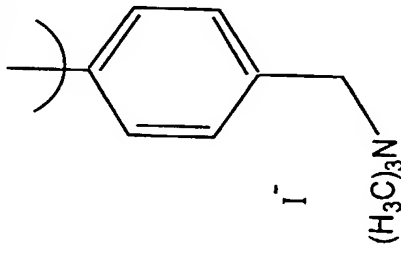
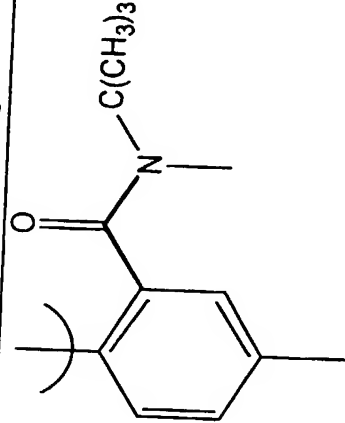
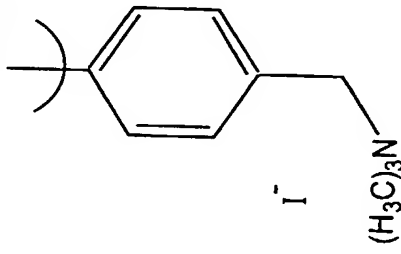
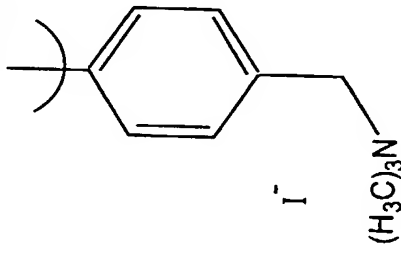
| | | | | | |
|--|---------|---------|----|---|-----------------|
| 1313 | n-butyl | ethyl | OH | H | phenyl |
| 1314 | ethyl | n-butyl | OH | H | phenyl |
| 1315 | ethyl | n-butyl | OH | H | phenyl |
| 1316 | n-butyl | ethyl | OH | H | phenyl |
| 1317 | n-butyl | ethyl | OH | H | phenyl |
| 1318 | ethyl | n-butyl | OH | H | phenyl |
| 1319 | ethyl | n-butyl | OH | H | 3-methoxyphenyl |
| 1320 | ethyl | n-butyl | OH | H | phenyl |
| 1321 | n-butyl | ethyl | OH | H | phenyl |
| 1322 | n-butyl | n-butyl | OH | H | |
|  | | | | | |
| 1323 | n-butyl | n-butyl | OH | H | |
|  | | | | | |

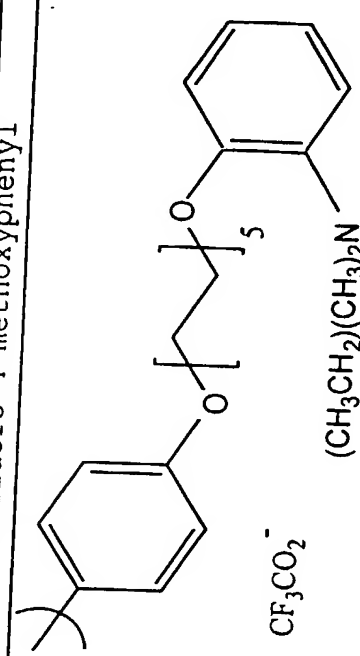
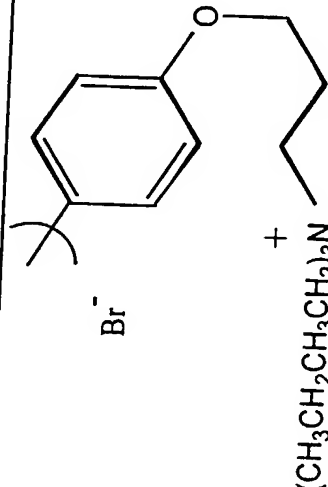
| | | | | | |
|------|---------|---------|----|---|--|
| 1324 | n-butyl | n-butyl | OH | H |  <p>4-((diethylamino)methyl)phenyl</p> |
| 1325 | n-butyl | n-butyl | OH | H | |
| 1326 | n-butyl | n-butyl | OH | H |  <p>3-fluoro-4-hydroxy-5-iodophenyl</p> |
| 1327 | n-butyl | n-butyl | OH | H | |
| 1328 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|---|
| 1329 | n-butyl | n-butyl | OH | H |  |
| 1330 | n-butyl | n-butyl | OH | H |  |

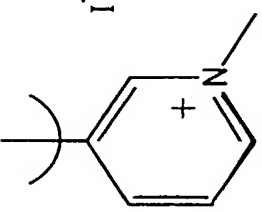
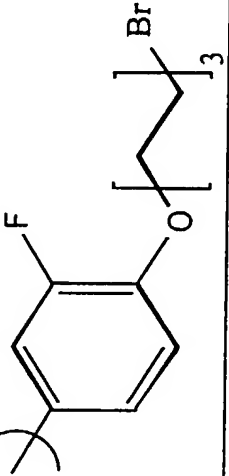
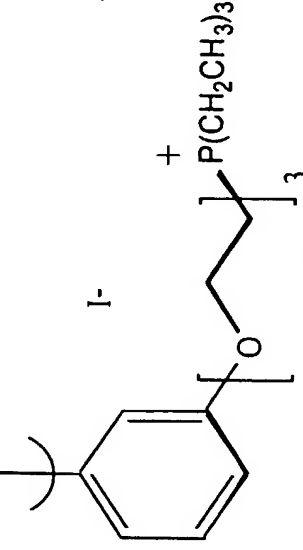
| | | | | | |
|------|---------|---------|----|---|---|
| 1331 | n-butyl | n-butyl | OH | H |  |
| 1332 | n-butyl | n-butyl | OH | H |  |
| 1333 | n-butyl | n-butyl | OH | H |  |

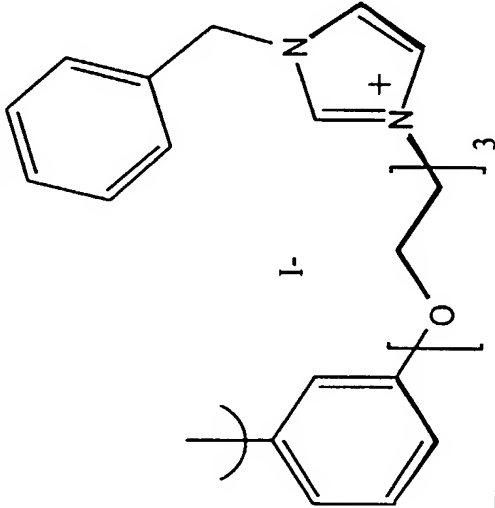
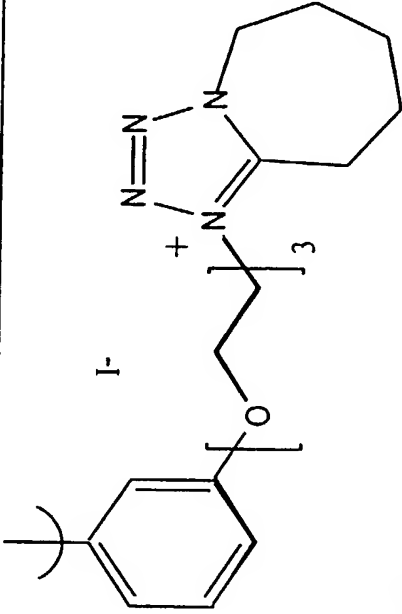
| | | | | | |
|------|---------|---------|----|---|--|
| 1334 | n-butyl | n-butyl | OH | H | |
| 1335 | n-butyl | n-butyl | OH | H | |
| 1336 | n-butyl | n-butyl | OH | H | |

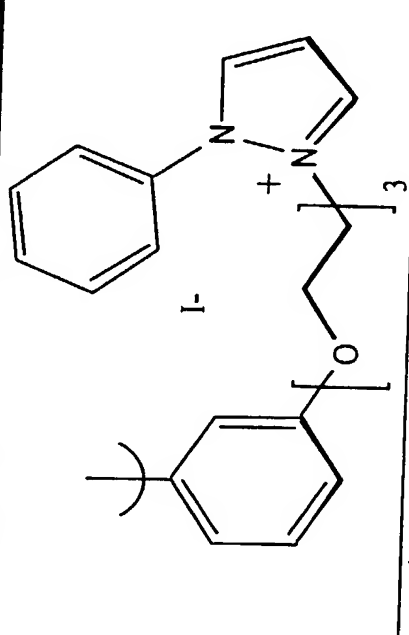
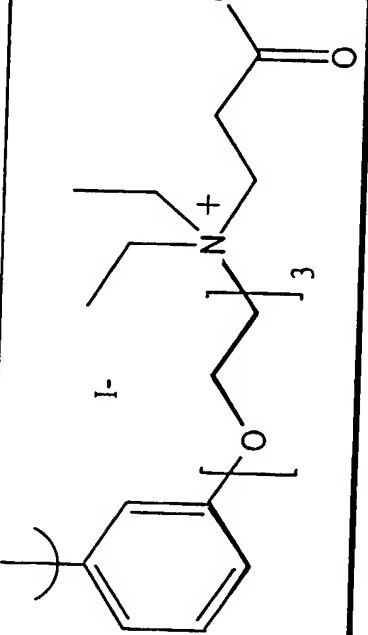
| | | | | | |
|------|---------|---------|--------|---|---|
| I337 | n-butyl | n-butyl | OH | H |  |
| I338 | n-butyl | n-butyl | OH | H |  |
| I339 | n-butyl | n-butyl | OH | H |  |
| I340 | n-butyl | ethyl | OH | H |  |
| I341 | n-butyl | n-butyl | acetox | H |  |
| I342 | n-butyl | n-butyl | y | H |  |
| I343 | ethyl | n-butyl | OH | H |  |

| | | | | | | |
|--|----------|----------|----------|----|---|---|
| I344 | n-butyl | n-butyl | n-butyl | OH | H | |
| I345 | ethyl | ethyl | n-butyl | OH | H | 3-fluoro-4-methoxyphenyl |
| I346 | ethyl | ethyl | n-butyl | OH | H | phenyl |
| I347 | n-butyl | n-butyl | n-butyl | OH | H | phenyl |
| I348 | isobutyl | isobutyl | isobutyl | OH | H | 3-fluoro-4-methoxyphenyl |
| I349 | ethyl | ethyl | n-butyl | OH | H | phenyl |
| I350 | n-butyl | n-butyl | n-butyl | OH | H | phenyl |
| I351 | n-butyl | n-butyl | n-butyl | OH | H | 3-fluoro-4-methoxyphenyl |
|  <p>CF₃CO₂⁻ (CH₃CH₂)(CH₃)₂N⁺</p> | | | | | | |
| I352 | n-butyl | n-butyl | n-butyl | OH | H |  <p>Br⁻ + (CH₃CH₂CH₃CH₂)₃N</p> |

| | | | | | |
|------|---------|---------|----|---|--|
| 1353 | n-butyl | n-butyl | OH | H | |
| 1354 | n-butyl | n-butyl | OH | H | |
| 1355 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|---|
| 1356 | n-butyl | n-butyl | OH | H |  |
| 1357 | n-butyl | n-butyl | OH | H |  |
| 1358 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|---|
| 1359 | n-butyl | n-butyl | OH | H |  |
| 1360 | n-butyl | n-butyl | OH | H |  |

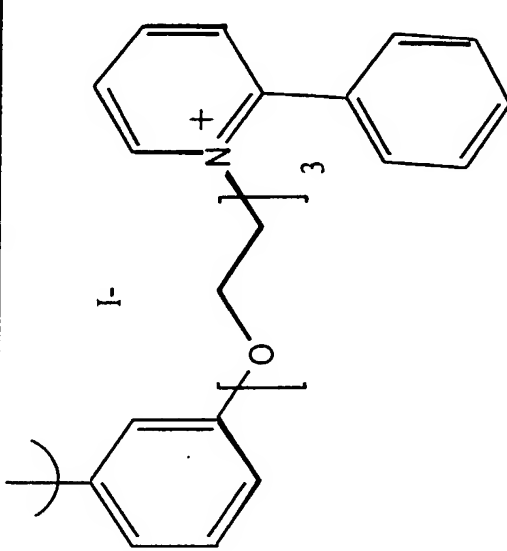
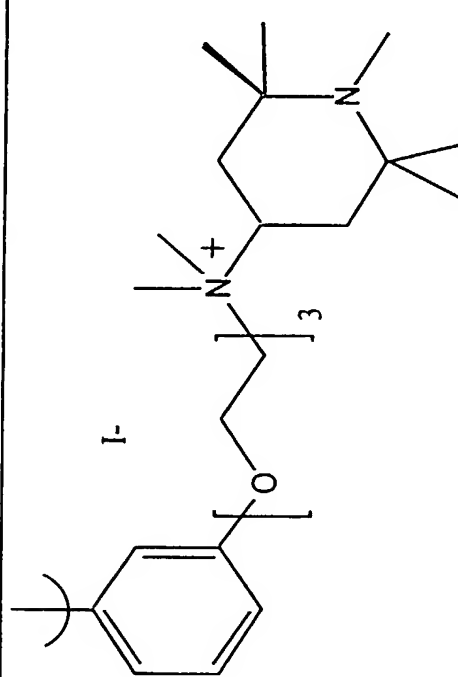
| | | | | | |
|------|---------|---------|----|---|--|
| I361 | n-butyl | n-butyl | OH | H |  <p>The structure shows a polymer chain consisting of a phenyl ring connected to an ether linkage, which is then connected to a pyridinium ring. The pyridinium ring is shown with a positive charge and a phenyl group. The polymer chain is represented by brackets with a subscript 3.</p> |
| I362 | n-butyl | n-butyl | OH | H |  <p>The structure shows a polymer chain consisting of a phenyl ring connected to an ether linkage, which is then connected to a carboxylic acid group. The carboxylic acid group is shown with a positive charge and a phenyl group. The polymer chain is represented by brackets with a subscript 3.</p> |

| | | | | | |
|------|---------|---------|----|---|--|
| 1363 | n-butyl | n-butyl | OH | H | |
| 1364 | n-butyl | n-butyl | OH | H | |
| 1365 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1366 | n-butyl | n-butyl | OH | H | |
| 1367 | n-butyl | n-butyl | OH | H | |
| 1368 | n-butyl | n-butyl | OH | H | |

SRL 6071
(C-3021/2)

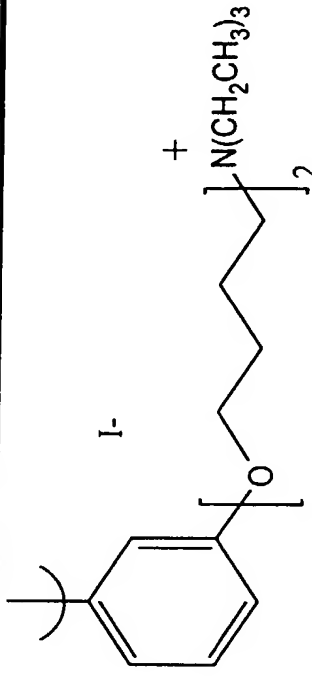
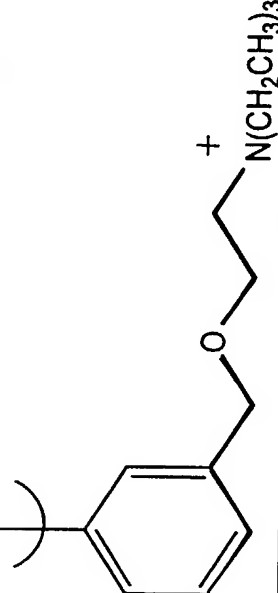
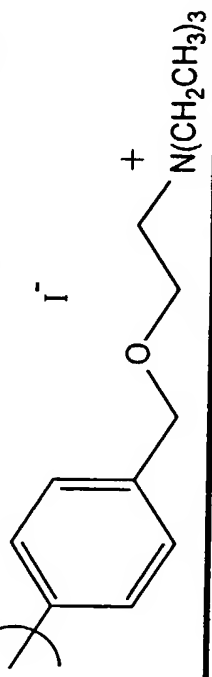
165

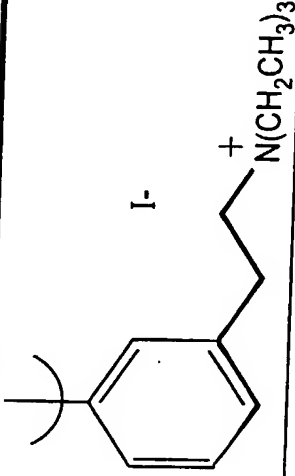
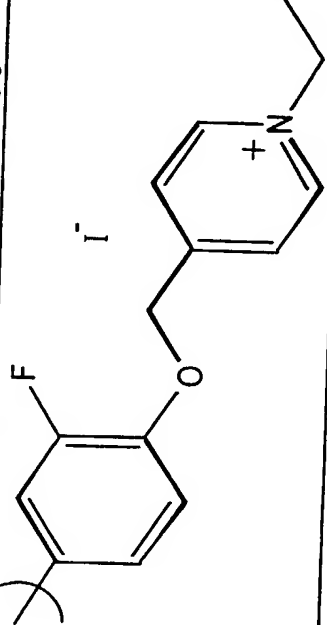
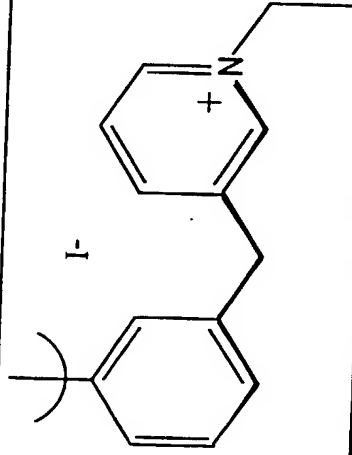
| | | | | | |
|------|---------|---------|----|---|---|
| 1369 | n-butyl | n-butyl | OH | H |  |
| 1370 | n-butyl | n-butyl | OH | H |  |

10068297.020802

| | | | | | |
|------|---------|---------|----|---|---|
| 13/1 | n-butyl | n-butyl | OH | H | <p>Chemical structure of a polyether polymer. The repeating unit consists of a phenyl ring connected to an oxygen atom, which is part of a polymer chain. The chain is terminated by a 3-ethyl-1-methylbutyl cation (N⁺) and a 3-cyanopropyl anion (I⁻).</p> |
| 13/2 | n-butyl | n-butyl | OH | H | <p>Chemical structure of a polyether polymer. The repeating unit consists of a phenyl ring connected to an oxygen atom, which is part of a polymer chain. The chain is terminated by a 3-ethyl-1-methylbutyl cation (N⁺) and a 3-(dimethylamino)propyl anion (I⁻).</p> |
| 13/3 | n-butyl | n-butyl | OH | H | <p>Chemical structure of a polyether polymer. The repeating unit consists of a phenyl ring connected to an oxygen atom, which is part of a polymer chain. The chain is terminated by a 3-ethyl-1-methylbutyl cation (N⁺) and a 3-(diphenylphosphoryl)propyl anion (I⁻).</p> |

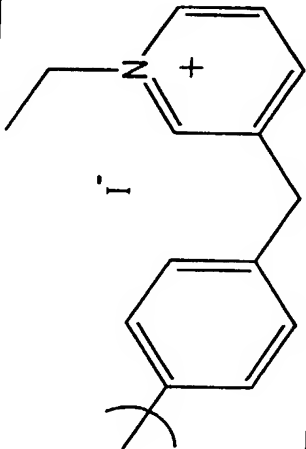
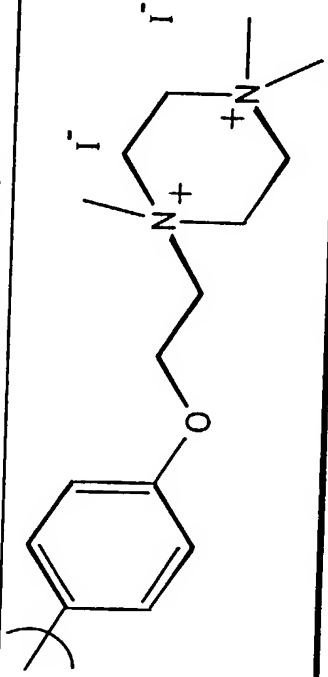
| | | | | | |
|------|---------|---------|----|---|--|
| 13/4 | n-butyl | n-butyl | OH | H | |
| 13/5 | n-butyl | n-butyl | OH | H | |
| 13/6 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|---|
| 1377 | n-butyl | n-butyl | OH | H |  |
| 1378 | n-butyl | n-butyl | OH | H |  |
| 1379 | n-butyl | n-butyl | OH | H |  |

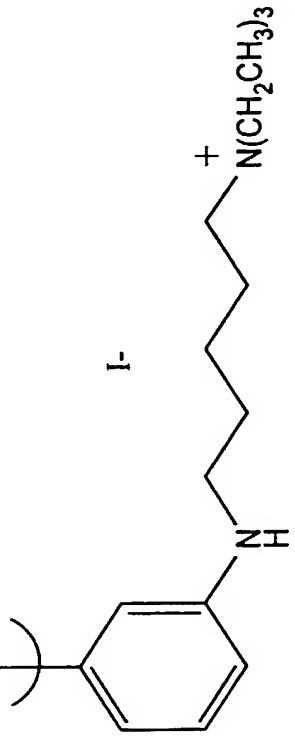
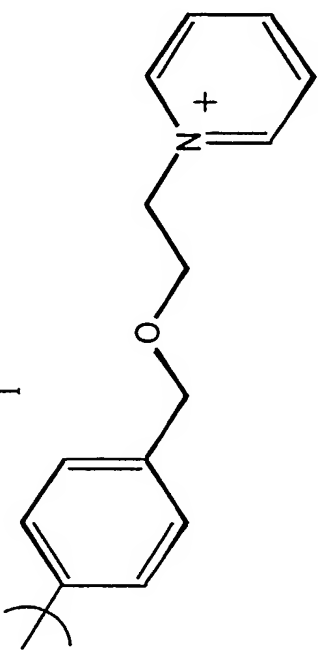
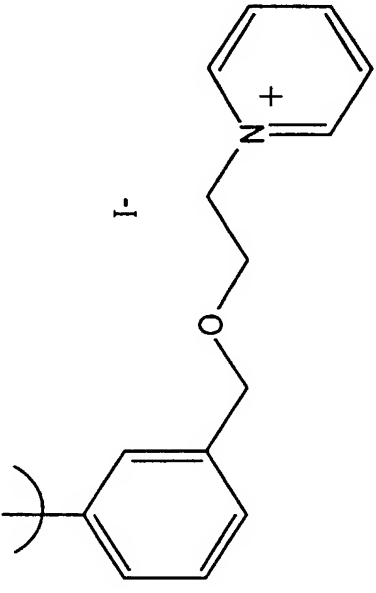
| | | | | | |
|------|---------|---------|----|---|---|
| 1380 | n-butyl | n-butyl | OH | H |  |
| 1381 | n-butyl | n-butyl | OH | H |  |
| 1382 | n-butyl | n-butyl | OH | H |  |

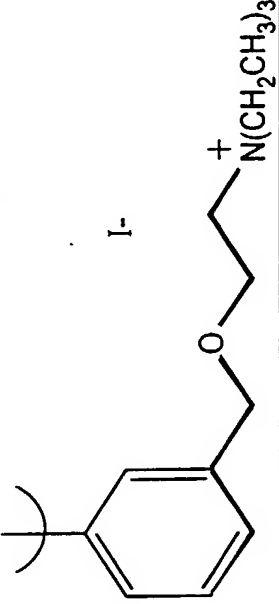
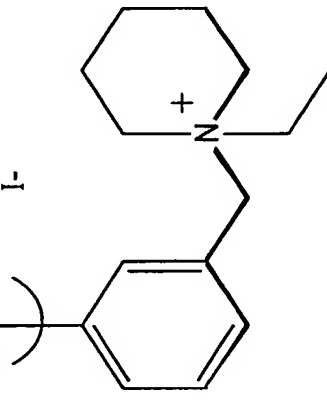
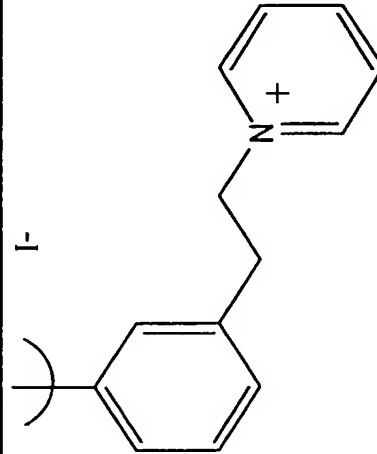
| | | | | | |
|------|---------|---------|----|---|--|
| 1383 | n-butyl | n-butyl | OH | H | |
| 1384 | n-butyl | n-butyl | OH | H | |
| 1385 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1386 | n-butyl | n-butyl | OH | H | |
| 1387 | n-butyl | n-butyl | OH | H | |
| 1388 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|---|
| 1389 | n-butyl | n-butyl | OH | H |  |
| 1390 | n-butyl | n-butyl | OH | H |  |

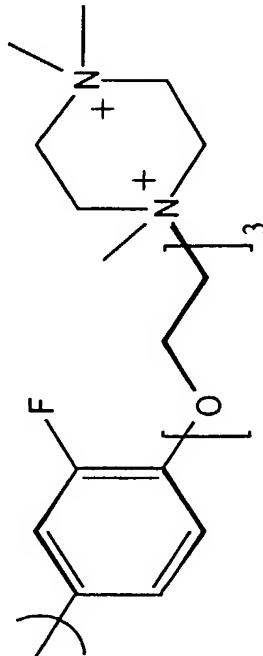
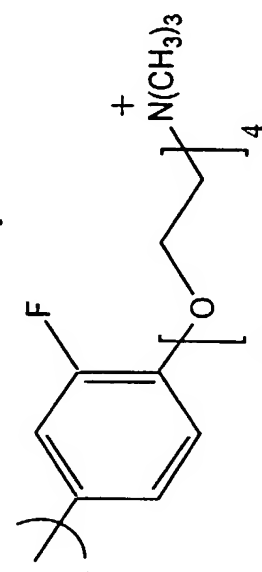
| | | | | | |
|------|---------|---------|----|---|--|
| I391 | n-butyl | n-butyl | OH | H | |
| I392 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1393 | n-butyl | n-butyl | OH | H |  |
| 1394 | n-butyl | n-butyl | OH | H |  |
| 1395 | n-butyl | n-butyl | OH | H |  |

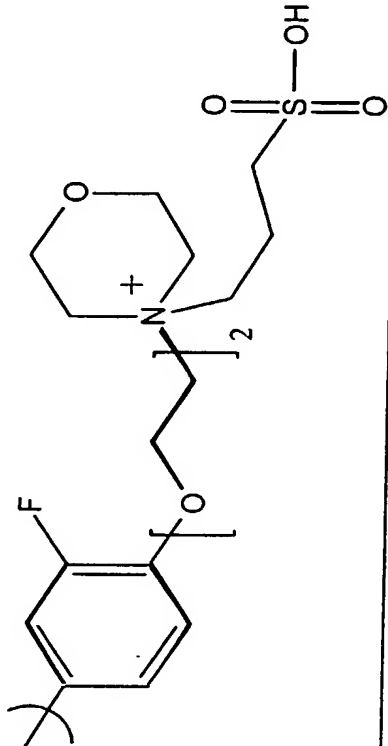
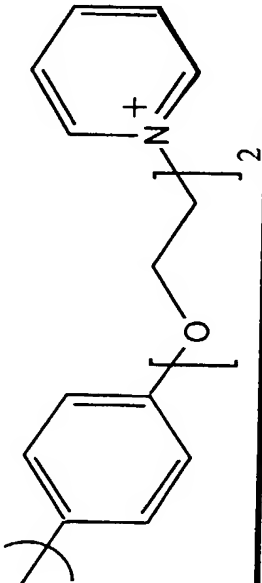
| | | | | | |
|------|---------|---------|----|---|--|
| 1396 | n-butyl | n-butyl | OH | H |  |
| 1397 | n-butyl | n-butyl | OH | H |  |
| 1398 | n-butyl | n-butyl | OH | H |  |

SRL 6071
(C-3021/2)

176

| | | | | | |
|------|---------|---------|----|---|--|
| 1399 | n-butyl | n-butyl | OH | H |  |
| 1400 | n-butyl | n-butyl | OH | H |  |

10068297 .020902

| | | | | | |
|------|---------|---------|----|---|---|
| I401 | n-butyl | n-butyl | OH | H |  |
| I402 | n-butyl | n-butyl | OH | H |  |

SRL 6071
(C-3021/2)

178

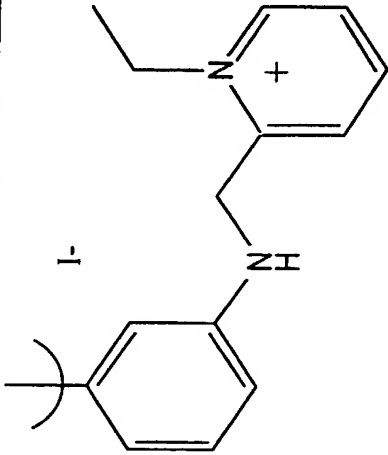
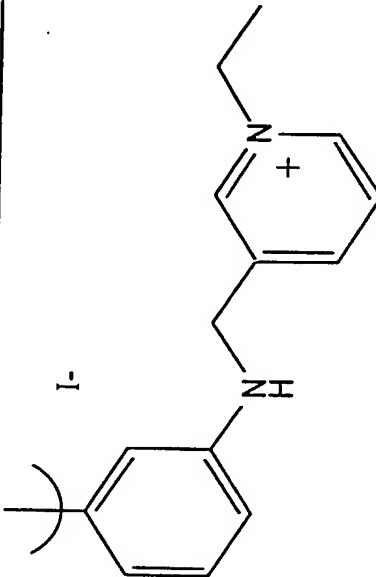
| | | | | | |
|------|---------|---------|----|---|--|
| I403 | n-butyl | n-butyl | OH | H | |
| I404 | n-butyl | n-butyl | OH | H | |
| I405 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1406 | n-butyl | n-butyl | OH | H | |
| 1407 | n-butyl | n-butyl | OH | H | |
| 1408 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1409 | n-butyl | n-butyl | OH | H | |
| 1410 | n-butyl | n-butyl | OH | H | |
| 1411 | n-butyl | n-butyl | OH | H | |

SRL 6071
(C-3021/2)

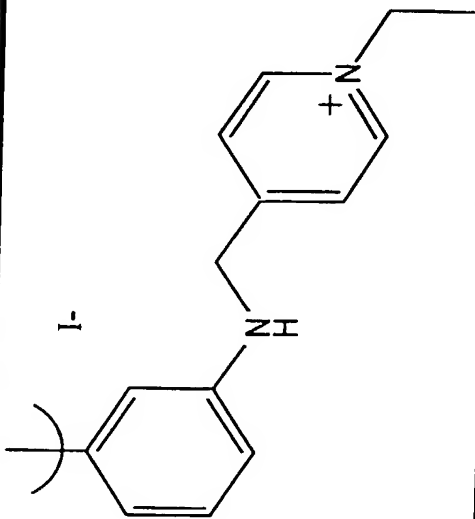
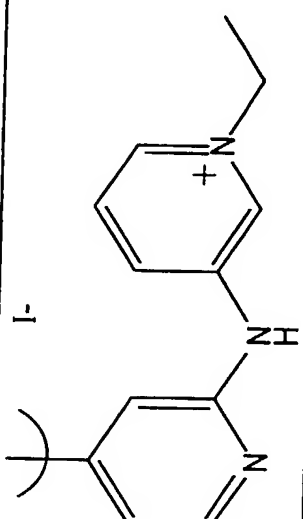
181

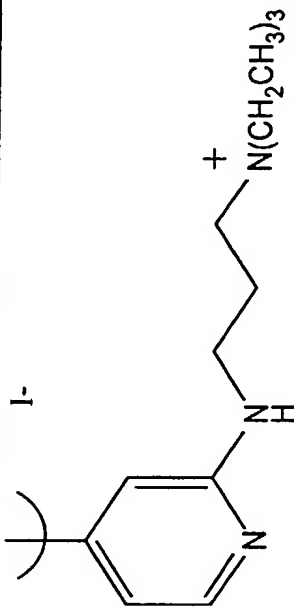
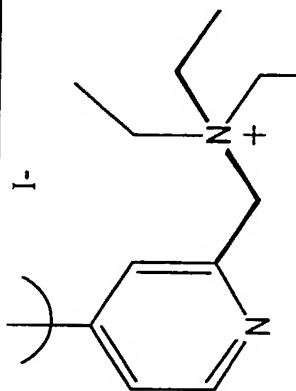
| | | | | | |
|------|---------|---------|----|---|---|
| I4I2 | n-butyl | n-butyl | OH | H |  |
| I4I3 | n-butyl | n-butyl | OH | H |  |

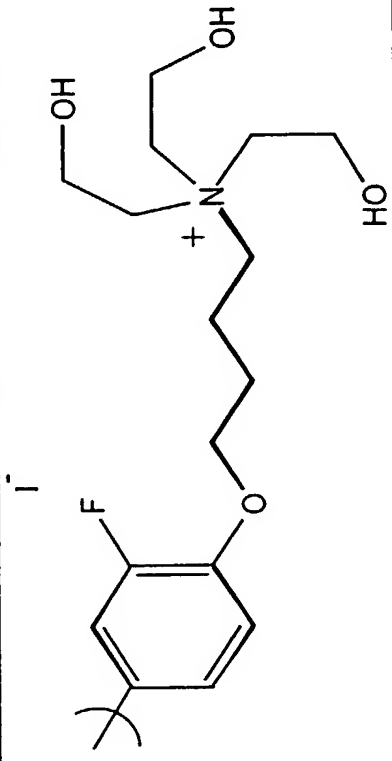
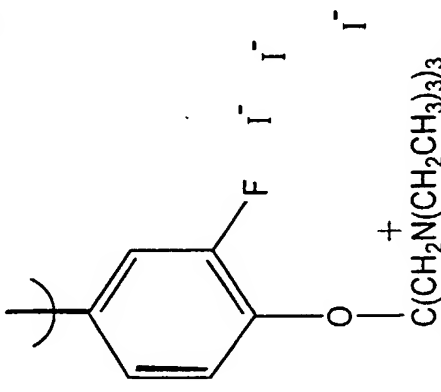
10068297 .020802

SRL 6071
(C-3021/2)

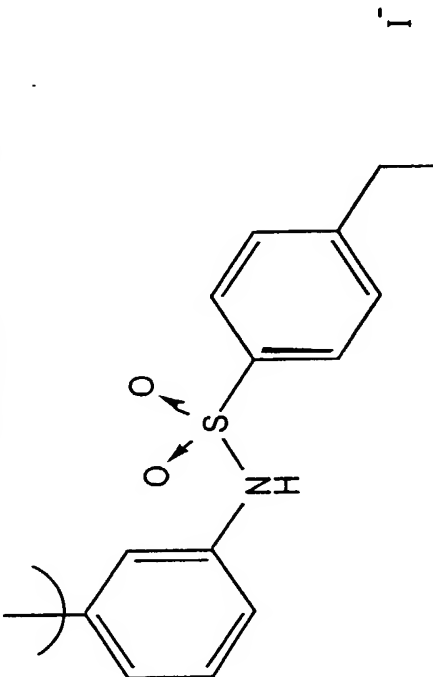
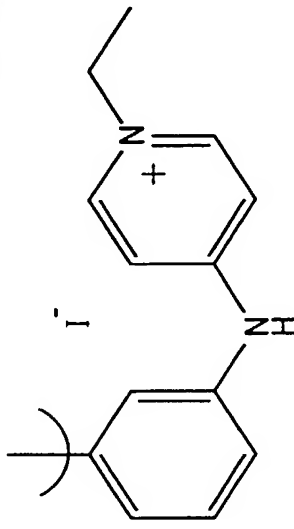
182

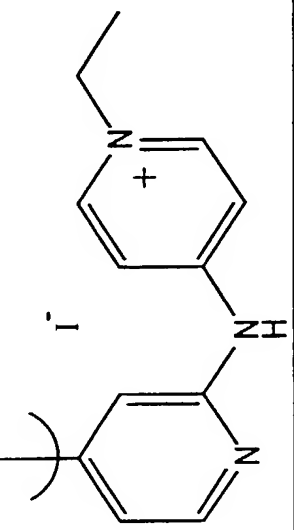
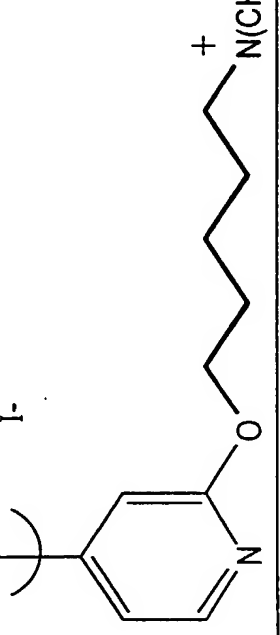
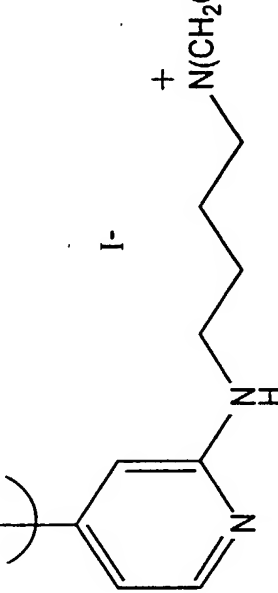
| | | | | | |
|------|---------|---------|----|---|---|
| 1414 | n-butyl | n-butyl | OH | H |  |
| 1415 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|--|
| 1416 | n-butyl | n-butyl | OH | H |  |
| 1417 | n-butyl | n-butyl | OH | H |  |

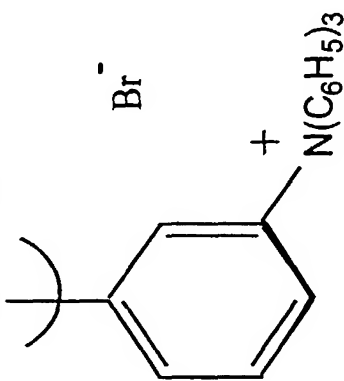
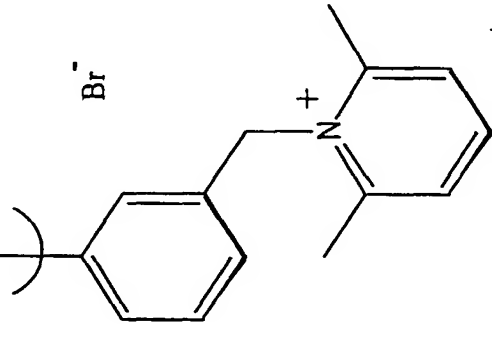
| | | | | | |
|------|---------|---------|----|---|--|
| I418 | n-butyl | n-butyl | OH | H |  |
| I419 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|--|
| I420 | n-butyl | n-butyl | OH | H | |
| I421 | n-butyl | n-butyl | OH | H | |

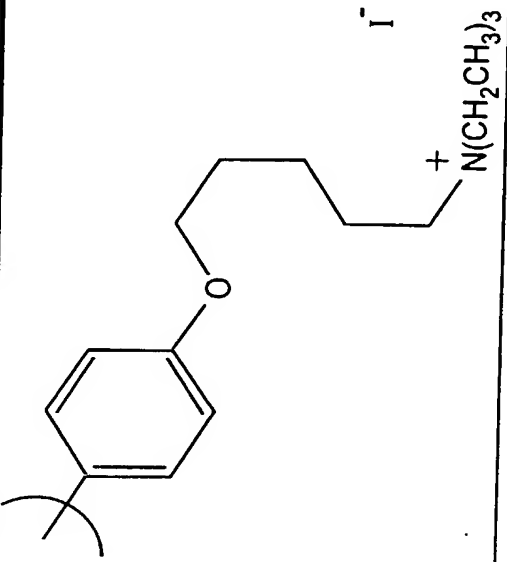
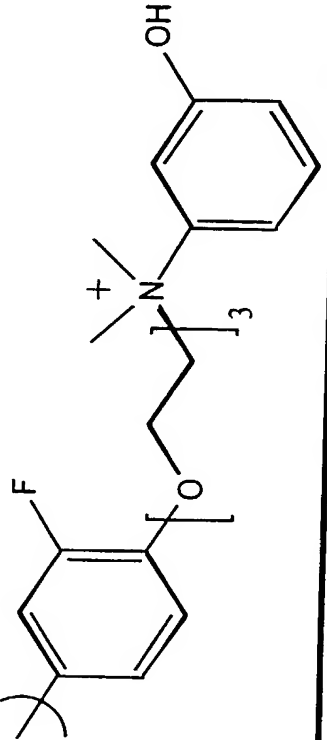
| | | | | | |
|------|---------|---------|----|---|---|
| I422 | n-butyl | n-butyl | OH | H |  $+ N(CH_2CH_3)_3$ |
| I423 | n-butyl | n-butyl | OH | H |  |

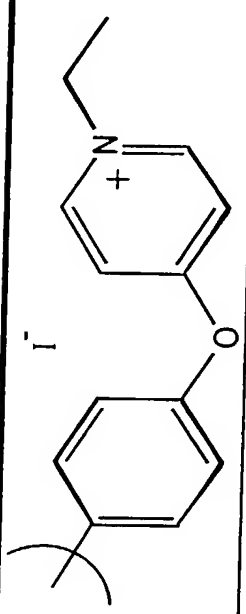
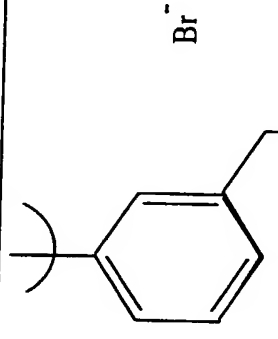
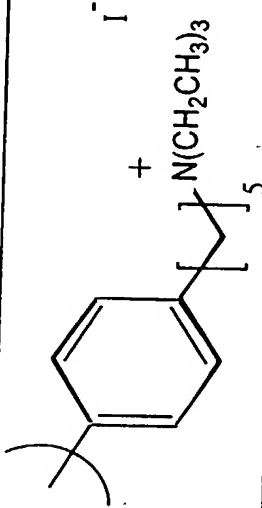
| | | | | | |
|------|---------|---------|----|---|---|
| I424 | n-butyl | n-butyl | OH | H |  |
| I425 | n-butyl | n-butyl | OH | H |  |
| I426 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|--|
| 1427 | n-butyl | n-butyl | OH | H | |
| 1428 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|--|
| 1429 | n-butyl | n-butyl | OH | H |  |
| 1430 | n-butyl | n-butyl | OH | H |  |

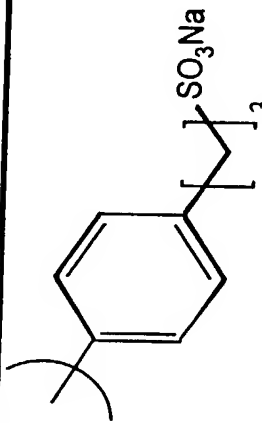
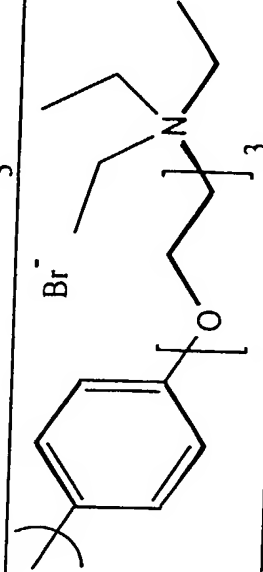
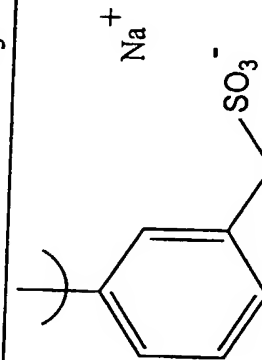
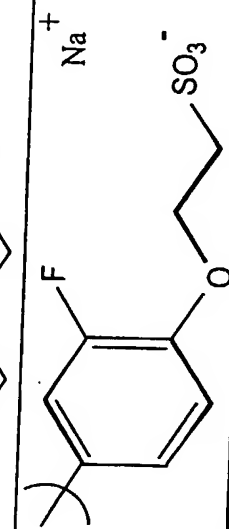
| | | | | | |
|------|---------|---------|----|---|--|
| I431 | n-butyl | n-butyl | OH | H | |
| I432 | n-butyl | n-butyl | OH | H | |
| I433 | n-butyl | n-butyl | OH | H | |

| | | | | | |
|------|---------|---------|----|---|---|
| 1434 | n-butyl | n-butyl | OH | H |  |
| 1435 | n-butyl | n-butyl | OH | H |  |

| | | | | | |
|------|---------|---------|----|---|---|
| 1436 | n-butyl | n-butyl | OH | H |  |
| 1437 | n-butyl | n-butyl | OH | H |  |
| 1438 | n-butyl | n-butyl | OH | H |  |

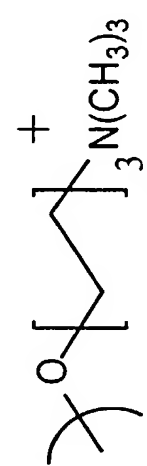
| | | | | | |
|------|---------|---------|----|---|--|
| I439 | n-butyl | n-butyl | OH | H | |
| I440 | n-butyl | n-butyl | OH | H | |
| I441 | n-butyl | n-butyl | OH | H | |

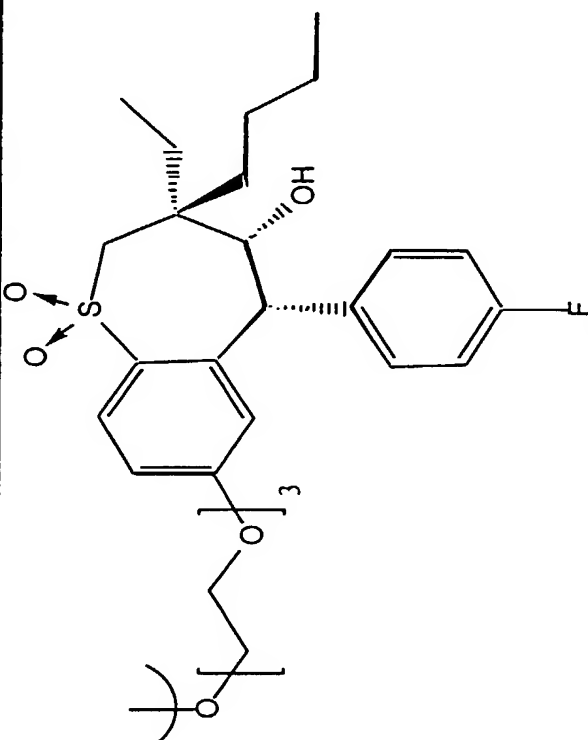
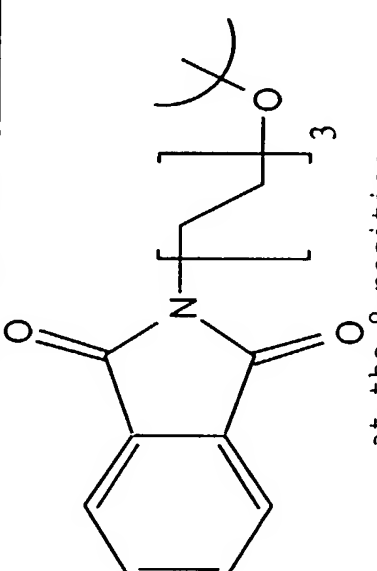
| | | | | | |
|------|---------|---------|----|---|--|
| 1442 | n-butyl | n-butyl | OH | H | |
| 1443 | n-butyl | n-butyl | OH | H | |
| 1444 | n-butyl | n-butyl | OH | H | |

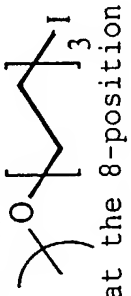
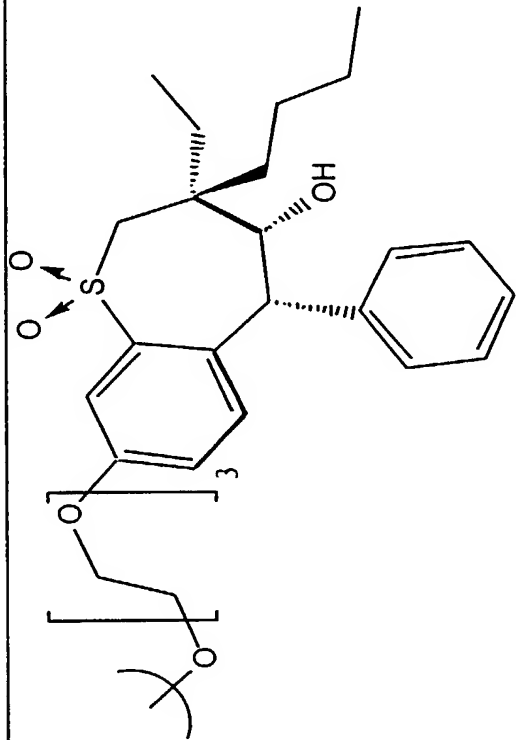
| | | | | | |
|------|---------|---------|----|---|--|
| 1445 | n-butyl | n-butyl | OH | H |  |
| 1446 | n-butyl | n-butyl | OH | H |  |
| 1447 | n-butyl | n-butyl | OH | H |  |
| 1448 | n-butyl | n-butyl | OH | H |  |

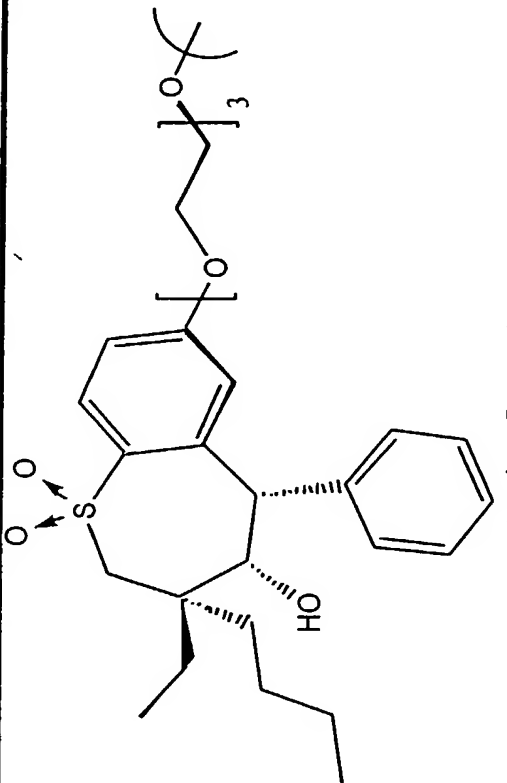
| | | | | | |
|------|---------|---------|----|---|--------|
| 1449 | n-butyl | n-butyl | OH | H | |
| 1450 | n-butyl | n-butyl | OH | H | phenyl |
| 1451 | n-butyl | n-butyl | OH | H | |

| Compound Number | R ⁶ | (R ^x) _q |
|-----------------|----------------|--------------------------------|
| I01 | H | |
| I02 | H | at the 7-position |
| I03 | H | /-trimethylammonium iodide |
| I04 | H | /-trimethylammonium iodide |
| I05 | H | /-dimethylamino |
| I06 | H | /-methanesulfonamido |
| I07 | H | /-(2'-bromoacetamido) |
| I08 | H | /-amino |
| I09 | H | /-(hexylamido) |
| I10 | H | /-amino |
| I11 | H | /-acetamido |
| I12 | H | /-amino |

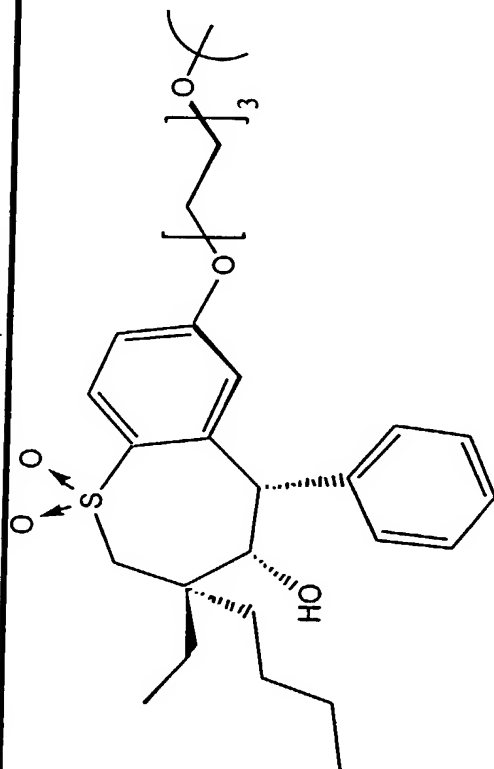
| | | |
|--|---|---------------------------|
| 112 | H | /-amino |
| 113 | H | /-amino |
| 114 | H | /-amino |
| 115 | H | /-(O-benzylcarbamato) |
| 116 | H | /-(O-benzylcarbamato) |
| 117 | H | /-(O-benzylcarbamato) |
| 118 | H | /-(O-benzylcarbamato) |
| 119 | H | /-(O-tert-butylcarbamato) |
| 120 | H | /-(O-benzylcarbamato) |
| 121 | H | /-amino |
| 122 | H | /-amino |
| 123 | H | /-hexylamino |
| 124 | H | /-(hexylamino) |
| 125 | H | I ⁻ |
|  <p>at the 8-position</p> | | |
| 126 | H | /-(O-benzylcarbamato) |
| 127 | H | /-amino |
| 128 | H | /-(O-benzylcarbamato) |
| 129 | H | /-amino |

| | | |
|-----|---|--|
| 131 | H |  <p>at the 7-position</p> |
| 132 | H |  <p>at the 8-position</p> |

| | | |
|-----|---|--|
| I33 | H | 8-(hexyloxy) |
| I34 | H |  <p>at the 8-position</p> |
| I35 | H |  <p>at the 8-position 8-hydroxy</p> |
| I36 | H | |

| | | |
|-----|---|---|
| I37 | H |  <p>at the 7-position 8-acetoxy</p> |
| I38 | H | |

| | | | |
|-----|---------------------------|--|-------------------|
| 139 | H | | |
| 140 | | | |
| 141 | | | |
| 142 | 3-methoxy-phenyl | | |
| 143 | H | | /-methylmercapto |
| 144 | H | | /-methylmercapto |
| 262 | H | | /- (N-azetidinyl) |
| 263 | 3-methoxy-phenyl | | /-methoxy |
| 264 | H | | /-methoxy |
| 265 | 3-trifluoro-methyl-phenyl | | /-methoxy |
| 266 | H | | /-hydroxy |



at the 7-position

| | | |
|-----|------------------|-----------------------|
| 267 | H | /-methoxy |
| 268 | H | /-methoxy |
| 269 | 4-fluoro-phenyl | /-methoxy |
| 270 | H | /-hydroxy |
| 271 | H | /-bromo |
| 272 | 3-methoxy-phenyl | /-bromo |
| 273 | 4-fluoro-phenyl | /-fluoro |
| 274 | H | /-fluoro |
| 275 | 3-methoxy-phenyl | /-fluoro |
| 276 | H | /-fluoro |
| 277 | H | /-methoxy |
| 278 | H | /-methoxy |
| 279 | H | /-methoxy |
| 280 | H | /-methoxy |
| 281 | H | /-methylmercapto |
| 282 | H | /-methyl |
| 283 | 4-fluoro-phenyl | /-methyl |
| 284 | H | /-(4'-morpholino) |
| 286 | H | /-(O-benzylcarbamato) |
| 287 | H | /-amino |
| 288 | H | /-amino |
| 289 | H | /-amino |
| 290 | H | /-amino |
| 291 | H | /-(O-benzylcarbamato) |
| 292 | H | /-amino |

| | | |
|------|---|----------------------------|
| 293 | H | /-benzylamino |
| 294 | H | /-dimethylamino |
| 295 | H | /-amino |
| 296 | H | /-amino |
| 1000 | H | /-dimethylamino |
| 1001 | H | /-dimethylamino |
| 1002 | H | /-dimethylamino |
| 1003 | H | /-dimethylamino |
| 1004 | H | /-dimethylamino |
| 1005 | H | /-dimethylamino |
| 1006 | H | /-dimethylamino |
| 1007 | H | /-dimethylamino |
| 1008 | H | /-dimethylamino |
| 1009 | H | /-dimethylamino |
| 1010 | H | /-dimethylamino |
| 1011 | H | /-dimethylamino |
| 1012 | H | /-dimethylamino; 9-methoxy |
| 1013 | H | /-dimethylamino |
| 1014 | H | /-dimethylamino; 9-methoxy |
| 1015 | H | /-dimethylamino |
| 1016 | H | /-dimethylamino |
| 1017 | H | /-dimethylamino |
| 1018 | H | /-dimethylamino |
| 1019 | H | /-dimethylamino |
| 1020 | H | /-dimethylamino |
| 1021 | H | /-dimethylamino |
| 1022 | H | /-dimethylamino |
| 1023 | H | /-dimethylamino |
| 1024 | H | /-dimethylamino |

| | | |
|------|---|-----------------|
| I025 | H | /-dimethylamino |
| I026 | H | /-dimethylamino |
| I027 | H | /-dimethylamino |
| I028 | H | /-dimethylamino |
| I029 | H | /-dimethylamino |
| I030 | H | /-dimethylamino |
| I031 | H | /-dimethylamino |
| I032 | H | /-dimethylamino |
| I033 | H | /-dimethylamino |
| I034 | H | /-dimethylamino |
| I035 | H | /-dimethylamino |
| I036 | H | /-dimethylamino |
| I037 | H | /-dimethylamino |
| I038 | H | /-dimethylamino |
| I039 | H | /-dimethylamino |
| I040 | H | /-dimethylamino |
| I041 | H | /-dimethylamino |
| I042 | H | /-dimethylamino |
| I043 | H | /-dimethylamino |
| I044 | H | /-dimethylamino |
| I045 | H | /-dimethylamino |
| I046 | H | /-dimethylamino |
| I047 | H | /-dimethylamino |
| I048 | H | /-dimethylamino |
| I049 | H | /-dimethylamino |
| I050 | H | /-dimethylamino |
| I051 | H | /-dimethylamino |
| I052 | H | /-dimethylamino |
| I053 | H | /-dimethylamino |

| | | |
|------|---|-------------------------------------|
| I054 | H | /-dimethylamino |
| I055 | H | /-dimethylamino |
| I056 | H | /-dimethylamino |
| I057 | H | /-dimethylamino |
| I058 | H | /-dimethylamino |
| I059 | H | /-dimethylamino |
| I060 | H | /-methylamino |
| I061 | H | /-methylamino |
| I062 | H | /-methylamino |
| I063 | H | /-methylamino |
| I064 | H | /-methylamino |
| I065 | H | /-dimethylamino |
| I066 | H | /-dimethylamino |
| I067 | H | 9-dimethylamino |
| I068 | H | /-dimethylamino |
| I069 | H | /-dimethylamino; 9-dimethylamino |
| I070 | H | /-dimethylamino |
| I071 | H | /-dimethylamino |
| I072 | H | /-dimethylamino |
| I073 | H | /-dimethylamino |
| I074 | H | /-dimethylamino |
| I075 | H | /-dimethylamino; 9-dimethylamino |
| I076 | H | /-dimethylamino |
| I077 | H | /-dimethylamino |
| I078 | H | /-dimethylamino |
| I079 | H | /-dimethylamino |
| I080 | H | /-dimethylamino |
| I081 | H | /-dimethylamino |

| | | |
|------|---|-----------------|
| 1082 | H | /-dimethylamino |
| 1083 | H | /-dimethylamino |
| 1084 | H | /-dimethylamino |
| 1085 | H | /-dimethylamino |
| 1086 | H | /-dimethylamino |
| 1087 | H | /-dimethylamino |
| 1088 | H | /-dimethylamino |
| 1089 | H | /-dimethylamino |
| 1090 | H | /-dimethylamino |
| 1091 | H | /-dimethylamino |
| 1092 | H | /-dimethylamino |
| 1093 | H | /-dimethylamino |
| 1094 | H | /-dimethylamino |
| 1095 | H | /-dimethylamino |
| 1096 | H | /-dimethylamino |
| 1097 | H | /-dimethylamino |
| 1098 | H | /-dimethylamino |
| 1099 | H | /-dimethylamino |
| 1100 | H | /-dimethylamino |
| 1101 | H | /-dimethylamino |
| 1102 | H | /-dimethylamino |
| 1103 | H | /-dimethylamino |
| 1104 | H | /-dimethylamino |
| 1105 | H | /-dimethylamino |
| 1106 | H | /-dimethylamino |
| 1107 | H | /-dimethylamino |
| 1108 | H | /-dimethylamino |
| 1109 | H | /-dimethylamino |
| 1110 | H | /-dimethylamino |

10058297.020002

| | | |
|------|---|------------------------------|
| II11 | H | /-dimethylamino |
| II12 | H | /-dimethylamino |
| II13 | H | /-dimethylamino |
| II14 | H | /-methylamino |
| II15 | H | /-dimethylamino |
| II16 | H | /-dimethylamino |
| II17 | H | /-dimethylamino |
| II18 | H | /-dimethylamino |
| II19 | H | /-dimethylamino |
| II20 | H | /-dimethylamino |
| II21 | H | /-dimethylamino |
| II22 | H | /-dimethylamino |
| II23 | H | /-dimethylamino |
| II24 | H | /-dimethylamino |
| II25 | H | /-dimethylamino |
| II26 | H | /-dimethylamino |
| II27 | H | /-dimethylamino |
| II28 | H | /-dimethylamino |
| II29 | H | 9-dimethylamino |
| II30 | H | /-dimethylamino |
| II31 | H | /-dimethylamino |
| II32 | H | /-dimethylamino |
| II33 | H | /-dimethylamino |
| II34 | H | /-dimethylamino |
| II35 | H | /-dimethylamino |
| II36 | H | /-dimethylamino |
| II37 | H | 9-(2',2''-dimethylhydrazino) |
| II38 | H | /-dimethylamino |
| II39 | H | /-dimethylamino |

| | | | |
|------|-----------------------------------|--|------------------------------------|
| 1140 | H | | /-(2',2'-dimethylhydrazino) |
| 1141 | H | | /-ethylmethylamino |
| 1142 | H | | /-dimethylamino |
| 1143 | 3-fluoro- 4-methoxy- phenyl | | /-dimethylamino |
| 1144 | H | | /-dimethylamino |
| 1145 | H | | 9-dimethylamino |
| 1146 | H | | /-dimethylamino |
| 1147 | H | | /-diethylamino |
| 1148 | H | | /-dimethylsulfonium, fluoride salt |
| 1149 | H | | /-ethylamino |
| 1150 | H | | /-ethylmethylamino |
| 1151 | H | | /-dimethylamino |
| 1152 | H | | /-(ethoxymethyl) methylamino |
| 1153 | H | | /-methylamino |
| 1154 | H | | 9-methoxy |
| 1155 | H | | /-methyl |
| 1156 | H | | /-methylmercapto |
| 1157 | H | | /-fluoro; 9-dimethylamino |
| 1158 | H | | /-methoxy |
| 1159 | H | | /-dimethylamino |
| 1160 | H | | /-diethylamino |
| 1161 | H | | /-dimethylamino |
| 1162 | H | | /-dimethylamino |
| 1163 | H | | /-methoxy |
| 1164 | H | | /-methoxy |
| 1165 | H | | /-trimethylammonium iodide |
| 1166 | H | | /-trimethylammonium iodide |

| | | |
|------|---|-----------------------------|
| 1167 | H | /-dimethylamino |
| 1168 | H | /-trimethylammonium iodide |
| 1169 | H | 8-dimethylamino |
| 1170 | H | /-ethylpropylamino |
| 1171 | H | /-dimethylamino |
| 1172 | H | /-methoxy |
| 1173 | H | /-ethylpropylamino |
| 1174 | H | /-phenyl |
| 1175 | H | /-methylsulfonyl |
| 1176 | H | 9-fluoro |
| 1177 | H | /-butylmethylamino |
| 1178 | H | /-dimethylamino |
| 1179 | H | 8-methoxy |
| 1180 | H | /-trimethylammonium iodide |
| 1181 | H | /-butylmethylamino |
| 1182 | H | /-methoxy |
| 1183 | H | /-fluoro |
| 1184 | H | /-fluoro; 9-fluoro |
| 1185 | H | /-fluoro |
| 1186 | H | /-fluoro; 9-fluoro |
| 1187 | H | /-methyl |
| 1188 | H | /-trimethylammonium iodide |
| 1189 | H | /-trimethylammonium iodide |
| 1190 | H | /-bromo |
| 1191 | H | /-hydroxy |
| 1192 | H | /-hydroxy |
| 1193 | H | /-dimethylamino |
| 1194 | H | /-dimethylamino |
| 1195 | H | /-(4'-methylpiperazin-1-yl) |


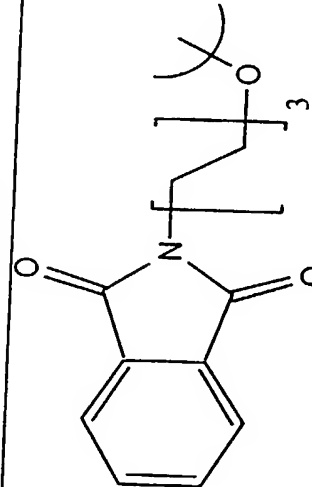
| | | |
|------|---------------------------|-------------------------|
| I196 | H | /-methoxy |
| I197 | H | /-(N-methylformamido) |
| I198 | H | /-methoxy |
| I199 | H | /-dimethylamino |
| I200 | phenyl | /-dimethylamino |
| I201 | H | /-methyl |
| I202 | H | /-methoxy |
| I203 | H | /-(4'-tert-butylphenyl) |
| I204 | H | /-methoxy |
| I205 | H | /-dimethylamino |
| I206 | H | /-dimethylamino |
| I207 | H | /-dimethylamino |
| I208 | H | /-dimethylamino |
| I209 | H | /-dimethylphenyl |
| I210 | H | /-dimethylamino |
| I211 | H | /-dimethylamino |
| I212 | H | 9-(4'-morpholino) |
| I213 | 3-fluoro-4-methoxy-phenyl | /-dimethylamino |
| I214 | H | /-(N-methylformamido) |
| I215 | H | 9-methylmercapto |
| I216 | H | /-bromo |
| I217 | H | /-dimethylamino |
| I218 | H | 9-methylsulfonyl |
| I219 | H | /-dimethylamino |
| I220 | H | /-isopropylamino |
| I221 | H | /-dimethylamino |
| I222 | H | /-ethylamino |
| I223 | H | 8-bromo; |


| | | |
|------|---|----------------------|
| 1224 | H | /-methyldiamino |
| 1225 | H | /-fluoro |
| 1226 | H | /-dimethyldiamino |
| 1227 | H | /-bromo |
| 1228 | H | /-(tert-butylamino |
| 1229 | H | 8-bromo; |
| 1230 | H | 7-dimethyldiamino |
| 1231 | H | /-dimethyldiamino |
| 1232 | H | 9-dimethyldiamino |
| 1233 | H | /-dimethyldiamino |
| 1234 | H | /-dimethyldiamino |
| 1235 | H | /-dimethyldiamino |
| 1236 | H | /-dimethyldiamino |
| 1237 | H | /-dimethyldiamino |
| 1238 | H | /-dimethyldiamino |
| 1239 | H | /-dimethyldiamino |
| 1240 | H | /-dimethyldiamino |
| 1241 | H | /-dimethyldiamino |
| 1242 | H | /-dimethyldiamino |
| 1243 | H | /-dimethyldiamino |
| 1244 | H | /-(1'-methyldiazido) |
| 1245 | H | /-dimethyldiamino |
| 1246 | H | /-dimethyldiamino |
| 1247 | H | /-dimethyldiamino |
| 1248 | H | /-dimethyldiamino |
| 1249 | H | /-dimethyldiamino |
| 1250 | H | /-dimethyldiamino |

AD

| | | |
|------|--------|--------------------------|
| I251 | H | /-dimethylamino |
| I252 | H | /-dimethylamino |
| I253 | H | /-dimethylamino |
| I254 | H | /-dimethylamino |
| I255 | H | /-dimethylamino |
| I256 | H | /-dimethylamino |
| I257 | H | 8-bromo; /-dimethylamino |
| I258 | H | 9-(tert-butylamino) |
| I259 | phenyl | /-dimethylamino |
| I260 | H | /-dimethylamino |
| I261 | H | /-dimethylamino |
| I262 | H | /-dimethylamino |
| I263 | H | /-bromo |
| I264 | H | /-isopropylamino |
| I265 | H | 9-isopropylamino |
| I266 | H | /-dimethylamino |
| I267 | H | /-carboxy, methyl ester |
| I268 | H | /-dimethylamino |
| I269 | H | /-dimethylamino |
| I270 | H | /-dimethylamino |
| I271 | H | /-dimethylamino |
| I272 | H | /-dimethylamino |
| I273 | H | /-dimethylamino |
| I274 | H | /-dimethylamino |
| I275 | H | /-dimethylamino |
| I276 | H | /-dimethylamino |
| I277 | H | /-dimethylamino |
| I278 | H | /-dimethylamino |
| I279 | H | /-dimethylamino |

| | | | |
|------|------------------|--|----------------------------|
| 1280 | H | | /-dimethylamino |
| 1281 | H | | /-dimethylamino |
| 1282 | H | | /-trimethylammonium iodide |
| 1283 | H | | /-dimethylamino |
| 1284 | H | | 9-ethylamino |
| 1285 | H | | /-dimethylamino |
| 1286 | H | | /-dimethylamino |
| 1287 | H | | /-dimethylamino |
| 1288 | H | | /-dimethylamino |
| 1289 | H | | /-dimethylamino |
| 1290 | H | | /-dimethylamino |
| 1291 | H | | /-dimethylamino |
| 1292 | H | | /-dimethylamino |
| 1293 | H | | /-dimethylamino |
| 1294 | H | | /-dimethylamino |
| 1295 | H | | /-dimethylamino |
| 1296 | H | | /-dimethylamino |
| 1297 | H | | /-dimethylamino |
| 1298 | H | | /-dimethylamino |
| 1299 | H | | /-dimethylamino |
| 1300 | phenyl | | /-dimethylamino |
| 1301 | H | | /-trimethylammonium iodide |
| 1302 | H | | 9-hydroxy |
| 1303 | H | | /-dimethylamino |
| 1304 | H | | /-tert-butylamino |
| 1305 | H | | 9-methylamino |
| 1306 | H | | /-dimethylamino |
| 1307 | 4-methoxy-phenyl | | 9-(4'-morpholino) |

| | | | |
|---|---|--|---|
| I308 | H | | |
| I309 | H | | /-dimethylamino |
| I310 | H | | 9-fluoro |
| I311 | H | | /-amino |
| I312 | H | | /-(hydroxylamino) |
| I313 | H | | 8-hexyloxy |
| I314 | H | | 8-ethoxy |
| I315 | H | | /-(hydroxylamino) |
| I316 | H | | /-(hexyloxy) |
| I317 | H | | 8-hydroxy |
| I ⁻ | | | |
| I318 | H | |  at the 8-position |
| I319 | H | | /-dimethylamino |
| I320 | H | | /-fluoro |
| I321 | H | | /-amino |
|  at the 8-position | | | |

| | | |
|------|---|--|
| I322 | H | /-dimethylamino |
| I323 | H | /-dimethylamino |
| I324 | H | /-dimethylamino |
| I325 | H | /-dimethylamino |
| I326 | H | /-dimethylamino |
| I327 | H | /-dimethylamino |
| I328 | H | /-dimethylamino |
| I329 | H | /-dimethylamino |
| I330 | H | /-dimethylamino |
| I331 | H | /-dimethylamino |
| I332 | H | /-dimethylamino |
| I333 | H | /-dimethylamino |
| I334 | H | /-dimethylamino |
| I335 | H | /-dimethylamino |
| I336 | H | /-dimethylamino |
| I337 | H | /-dimethylamino |
| I338 | H | /-(4'-methylpiperazinyl) |
| I339 | H | /-dimethylamino |
| I340 | H | /-methyl |
| I341 | H | /-dimethylamino |
| I342 | H | /-(4'-fluorophenyl) |
| I343 | H | /-amino |
| I344 | H | /-dimethylamino |
| I345 | H | /-trimethylammonium iodide |
| I346 | H |  |
| I347 | H | at the 8-position /-dimethylamino |

| | | |
|------|---|----------------------------|
| I348 | H | /-dimethylamino |
| I349 | H | /-dimethylamino |
| I350 | H | /-trimethylammonium iodide |
| I351 | H | /-dimethylamino |
| I352 | H | /-dimethylamino |
| I353 | H | /-dimethylamino |
| I354 | H | /-dimethylamino |
| I355 | H | /-dimethylamino |
| I356 | H | /-dimethylamino |
| I357 | H | /-dimethylamino |
| I358 | H | /-dimethylamino |
| I359 | H | /-dimethylamino |
| I360 | H | /-dimethylamino |
| I361 | H | /-dimethylamino |
| I362 | H | /-dimethylamino |
| I363 | H | /-dimethylamino |
| I364 | H | /-dimethylamino |
| I365 | H | /-dimethylamino |
| I366 | H | /-dimethylamino |
| I367 | H | /-dimethylamino |
| I368 | H | /-dimethylamino |
| I369 | H | /-dimethylamino |
| I370 | H | /-dimethylamino |
| I371 | H | /-dimethylamino |
| I372 | H | /-dimethylamino |
| I373 | H | /-dimethylamino |
| I374 | H | /-dimethylamino |
| I375 | H | /-dimethylamino |
| I376 | H | /-dimethylamino |

| | | |
|------|---|-----------------|
| 1377 | H | /-dimethylamino |
| 1378 | H | /-dimethylamino |
| 1379 | H | /-dimethylamino |
| 1380 | H | /-dimethylamino |
| 1381 | H | /-dimethylamino |
| 1382 | H | /-dimethylamino |
| 1383 | H | /-dimethylamino |
| 1384 | H | /-dimethylamino |
| 1385 | H | /-dimethylamino |
| 1386 | H | /-dimethylamino |
| 1387 | H | /-dimethylamino |
| 1388 | H | /-dimethylamino |
| 1389 | H | /-dimethylamino |
| 1390 | H | /-dimethylamino |
| 1391 | H | /-dimethylamino |
| 1392 | H | /-dimethylamino |
| 1393 | H | /-dimethylamino |
| 1394 | H | /-dimethylamino |
| 1395 | H | /-dimethylamino |
| 1396 | H | /-dimethylamino |
| 1397 | H | /-dimethylamino |
| 1398 | H | /-dimethylamino |
| 1399 | H | /-dimethylamino |
| 1400 | H | /-dimethylamino |
| 1401 | H | /-dimethylamino |
| 1402 | H | /-dimethylamino |
| 1403 | H | /-dimethylamino |
| 1404 | H | /-dimethylamino |
| 1405 | H | /-dimethylamino |

| | | |
|------|---|-----------------|
| I406 | H | /-dimethylamino |
| I407 | H | /-dimethylamino |
| I408 | H | /-dimethylamino |
| I409 | H | /-dimethylamino |
| I410 | H | /-dimethylamino |
| I411 | H | /-dimethylamino |
| I412 | H | /-dimethylamino |
| I413 | H | /-dimethylamino |
| I414 | H | /-dimethylamino |
| I415 | H | /-dimethylamino |
| I416 | H | /-dimethylamino |
| I417 | H | /-dimethylamino |
| I418 | H | /-dimethylamino |
| I419 | H | /-dimethylamino |
| I420 | H | /-dimethylamino |
| I421 | H | /-dimethylamino |
| I422 | H | /-dimethylamino |
| I423 | H | /-dimethylamino |
| I424 | H | /-dimethylamino |
| I425 | H | /-dimethylamino |
| I426 | H | /-dimethylamino |
| I427 | H | /-dimethylamino |
| I428 | H | /-dimethylamino |
| I429 | H | /-dimethylamino |
| I430 | H | /-dimethylamino |
| I431 | H | /-dimethylamino |
| I432 | H | /-dimethylamino |
| I433 | H | /-dimethylamino |
| I434 | H | /-dimethylamino |

| | | |
|------|---|----------------------|
| I435 | H | /-dimethylamino |
| I436 | H | /-dimethylamino |
| I437 | H | /-dimethylamino |
| I438 | H | /-dimethylamino |
| I439 | H | /-dimethylamino |
| I440 | H | /-dimethylamino |
| I441 | H | /-dimethylamino |
| I442 | H | /-dimethylamino |
| I443 | H | /-dimethylamino |
| I444 | H | /-dimethylamino |
| I445 | H | /-dimethylamino |
| I446 | H | /-methoxy; 8-methoxy |
| I447 | H | /-dimethylamino |
| I448 | H | /-dimethylamino |
| I449 | H | /-dimethylamino |

SRL 6071
(C-3021/2)

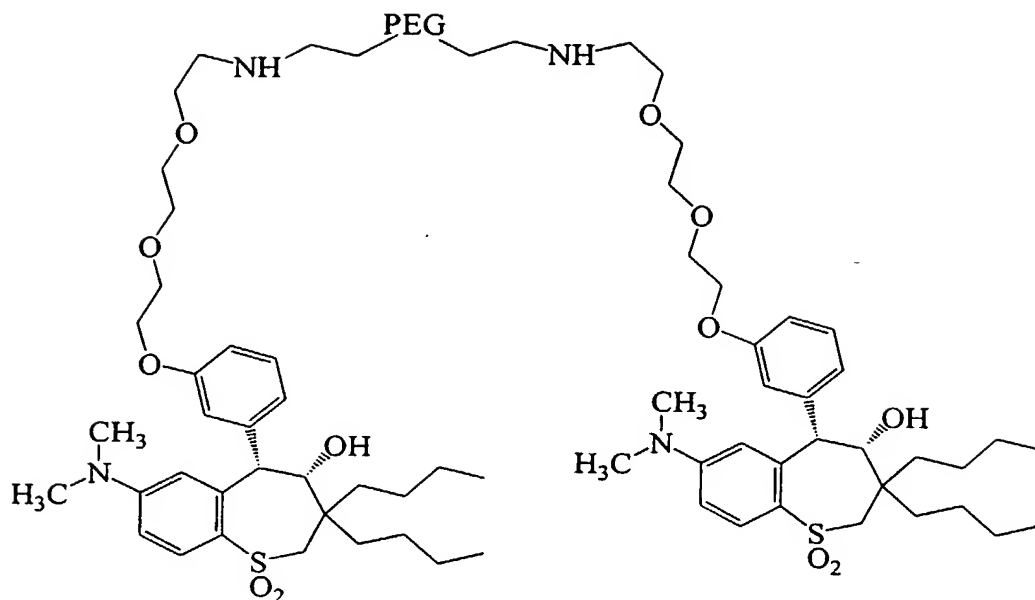
221

| | | |
|------|---|-----------------|
| I450 | H | /-dimethylamino |
| I451 | H | /-dimethylamino |

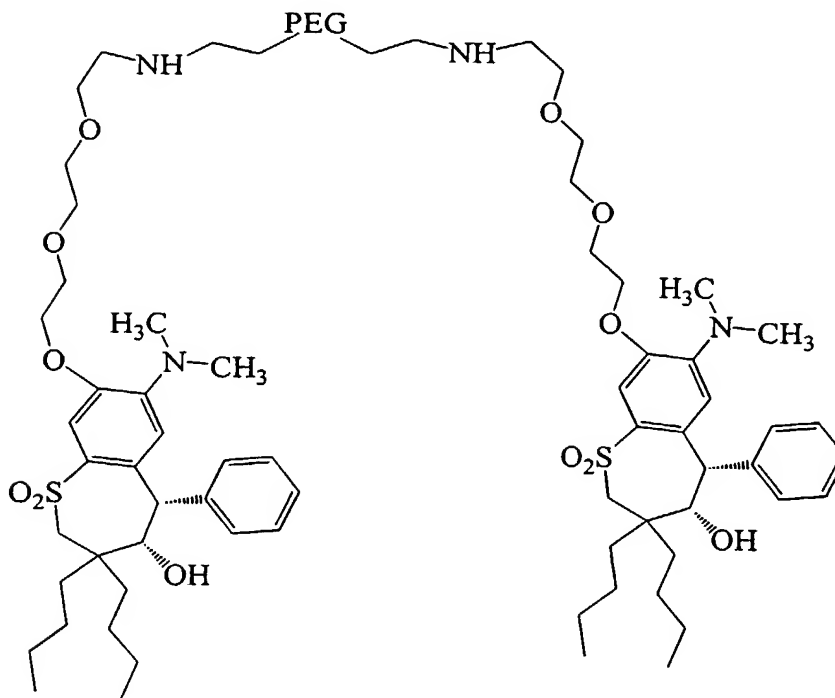
10068297 . 020802

SRL 6071
(C-3021/2)

222



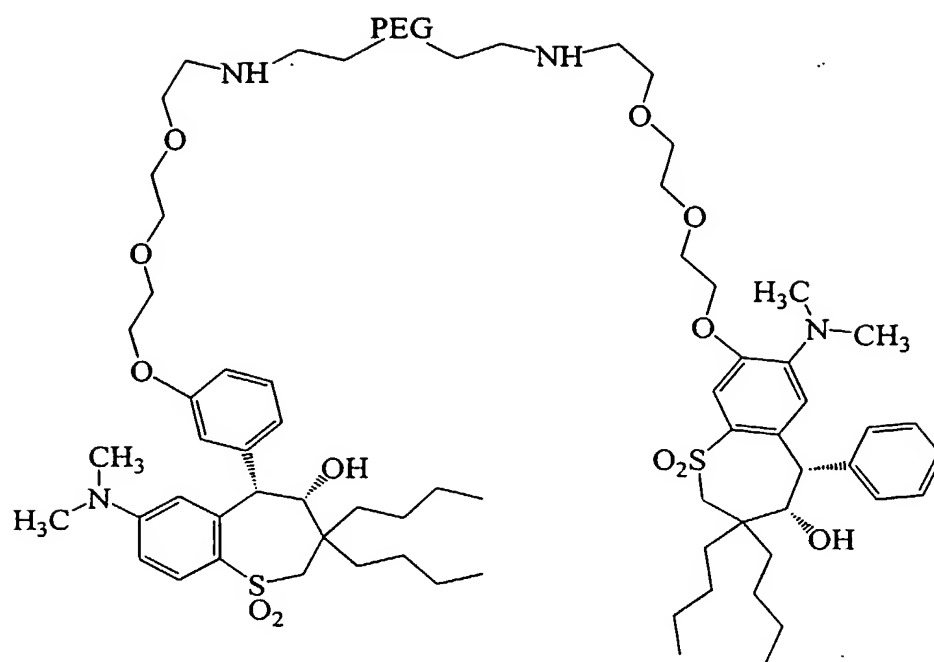
PEG = 3400 molecular weight polyethylene glycol polymer chain



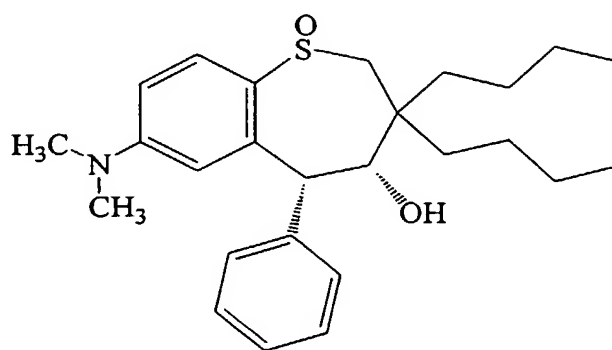
PEG = 3400 molecular weight polyethylene glycol polymer chain

SRL 6071
(C-3021/2)

223

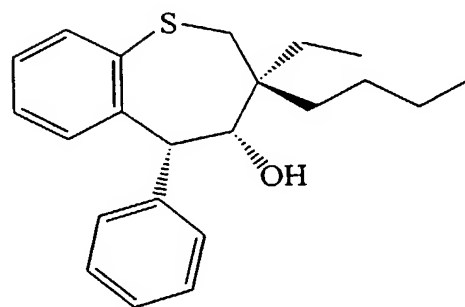
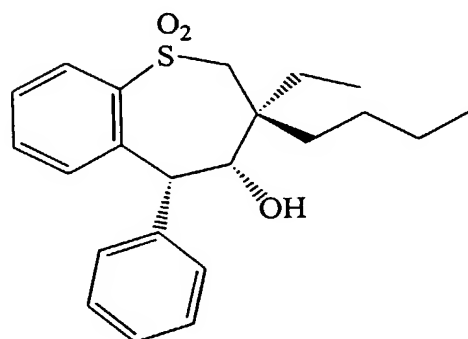
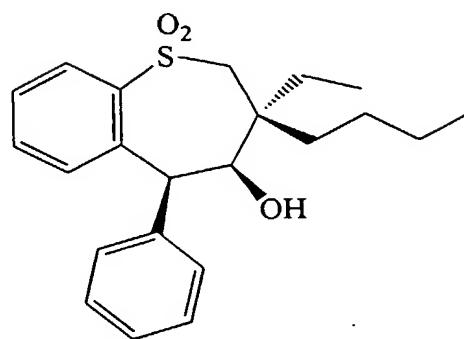
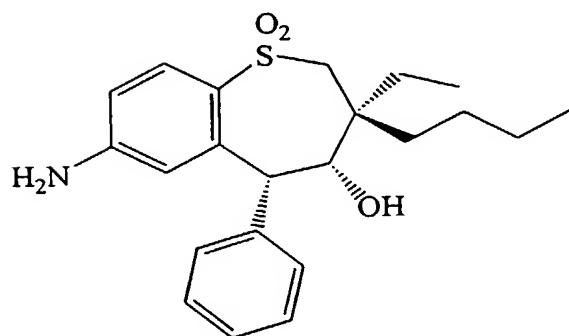
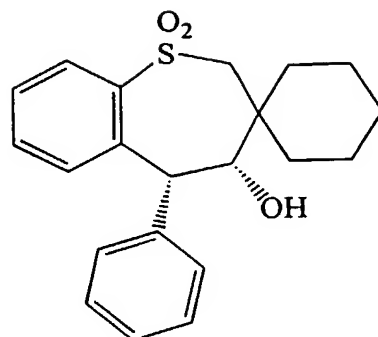
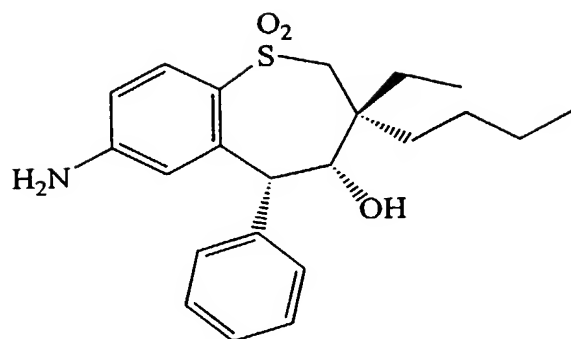


PEG = 3400 molecular weight polyethylene glycol polymer chain



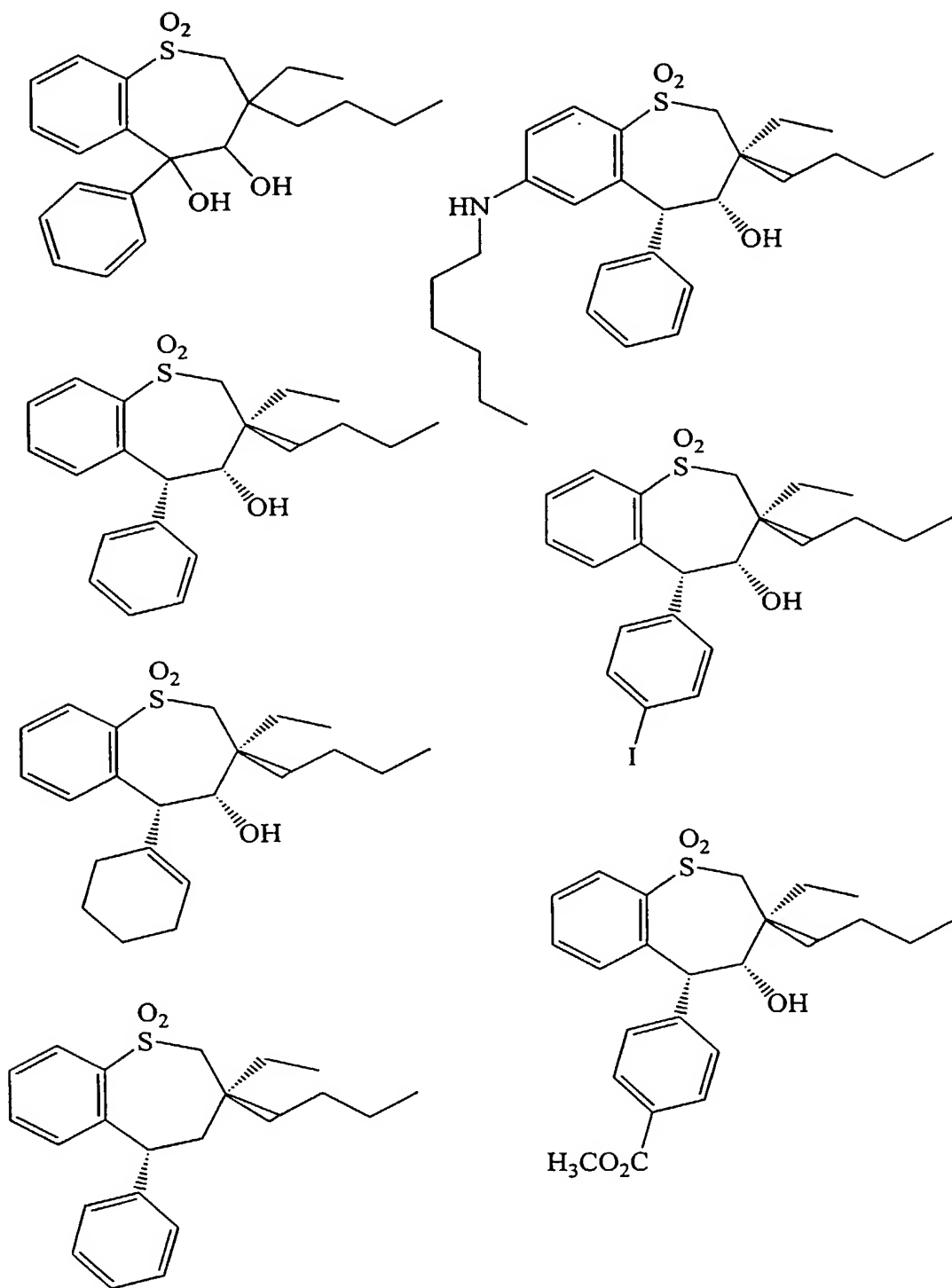
SRL 6071
(C-3021/2)

224



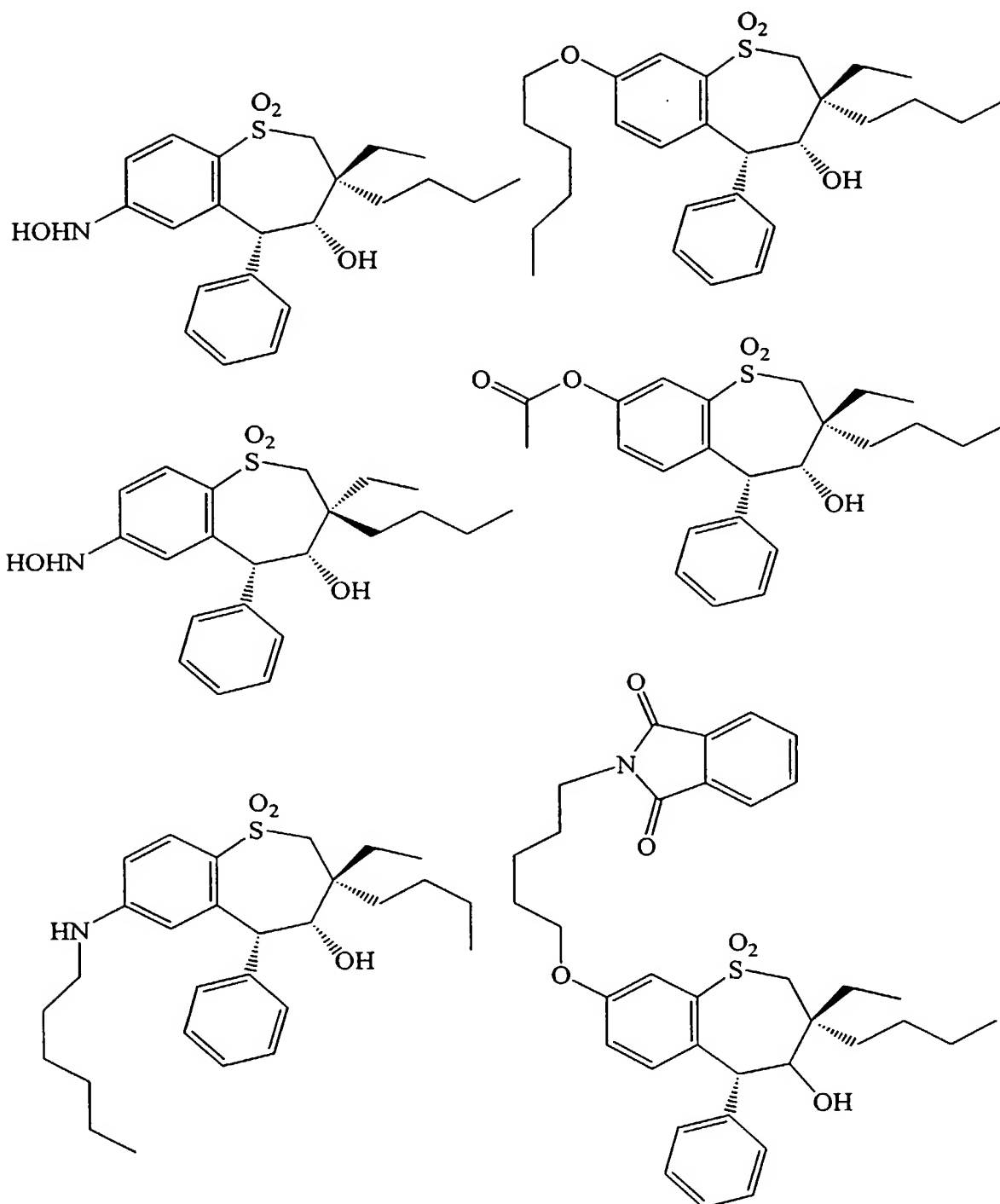
SRL 6071
(C-3021/2)

225



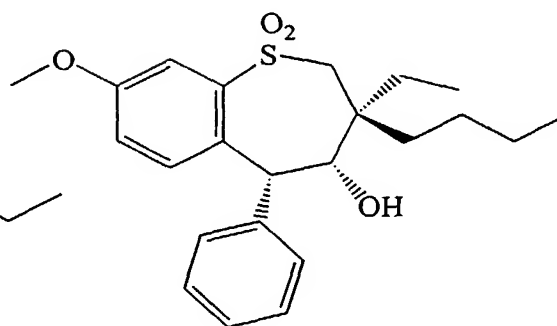
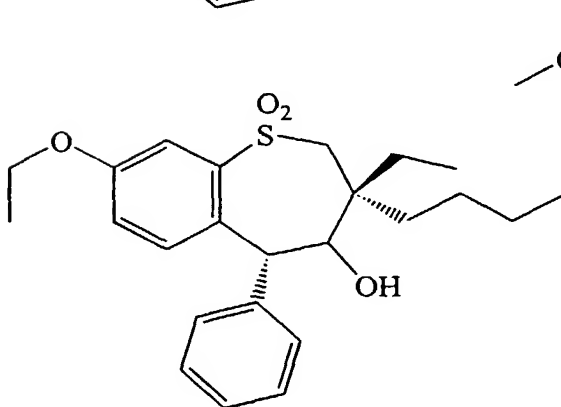
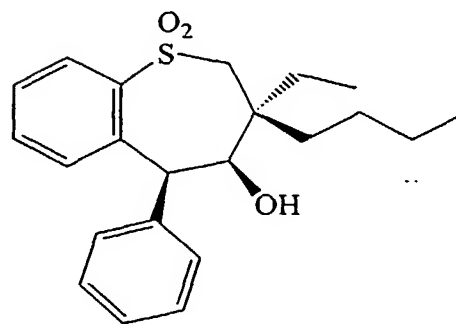
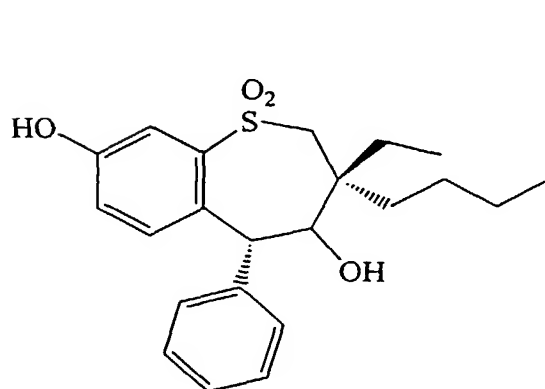
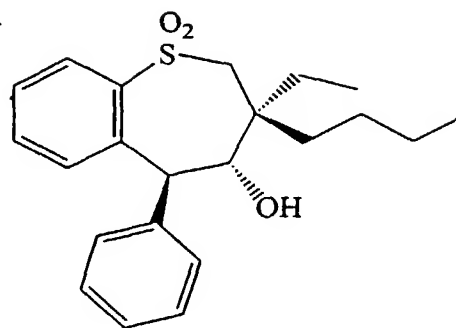
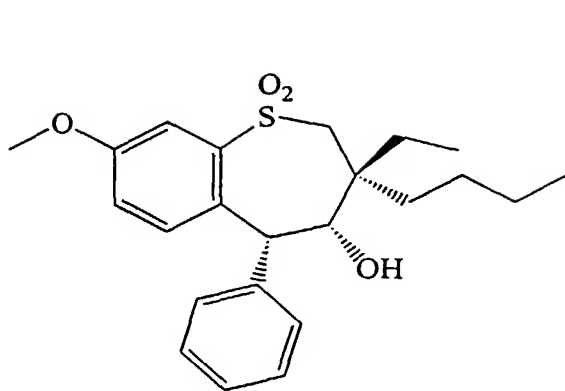
SRL 6071
(C-3021/2)

226



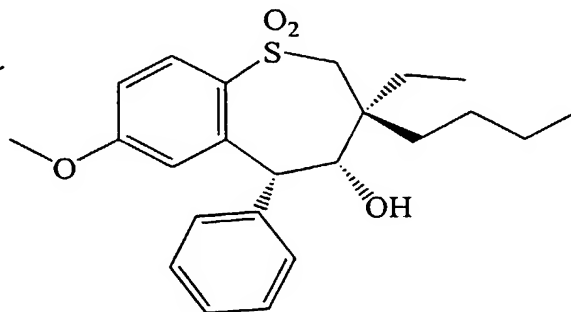
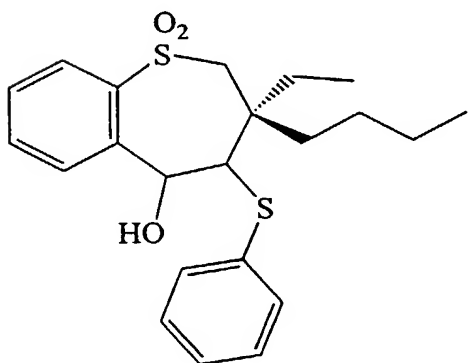
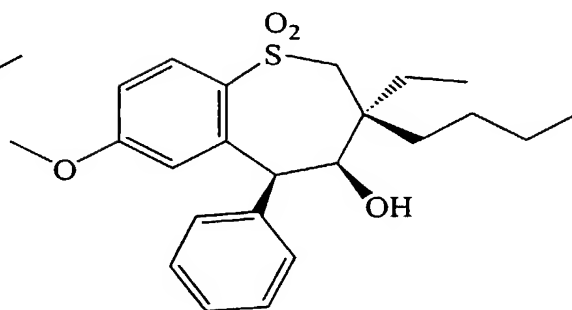
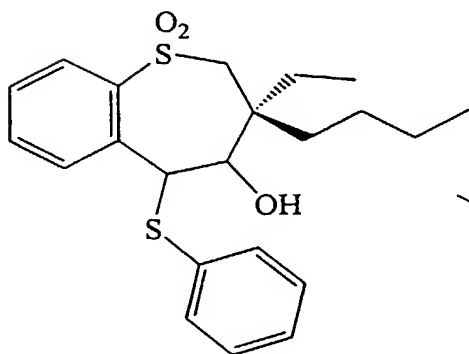
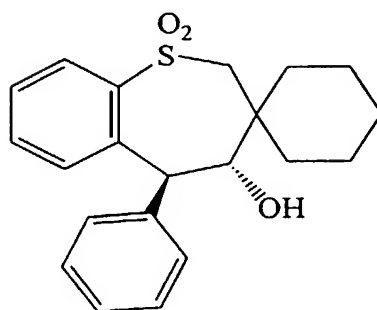
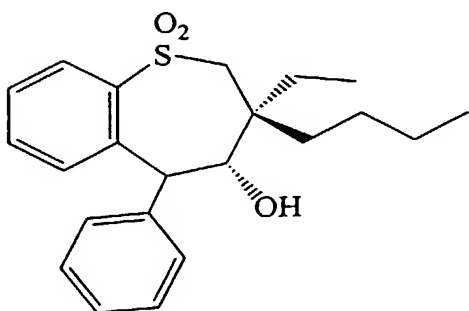
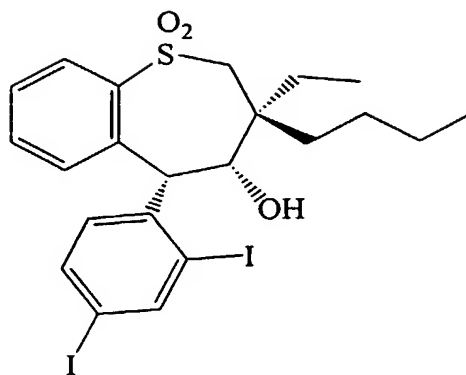
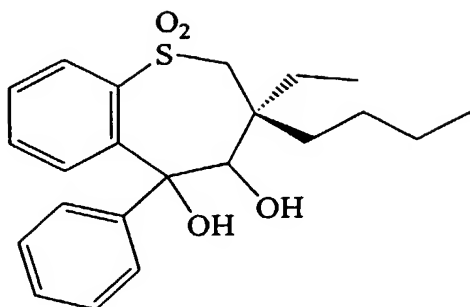
SRL 6071
(C-3021/2)

227



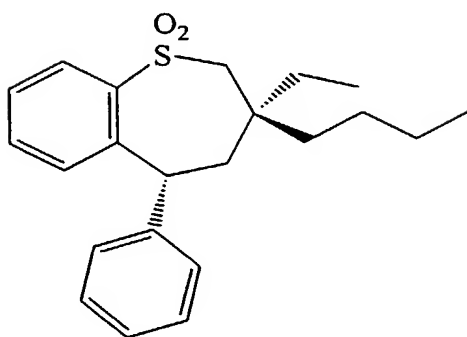
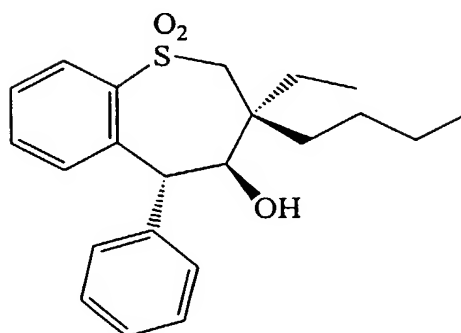
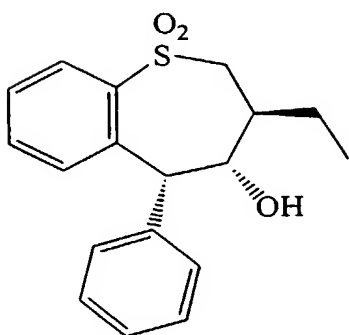
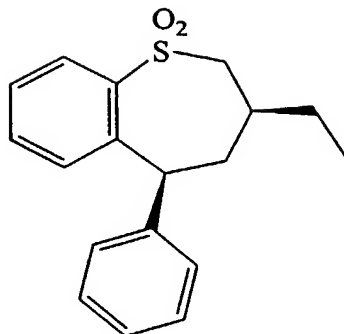
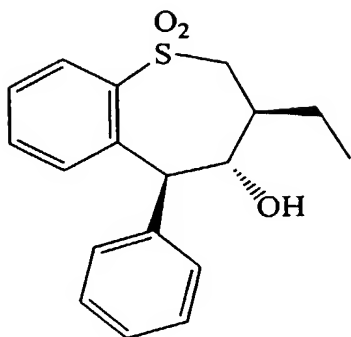
SRL 6071
(C-3021/2)

228



SRL 6071
(C-3021/2)

229



SRL 6071
(C-3021/2)

230

In further compounds of the present invention, R^5 and R^6 are independently selected from among hydrogen and ring-carbon substituted or unsubstituted aryl, thiophene, pyridine, pyrrole, thiazole, imidazole, pyrazole, 5 pyrimidine, morpholine, N-alkylpyridinium, N-alkylpiperazinium, N-alkylmorpholinium, or furan in which the substituent(s) are selected from among halo, hydroxyl, trihaloalkyl, alkoxy, amino, N-alkylamino, N,N-dialkylamino, quaternary ammonium salts, a C_1 to C_4 alkylene bridge having 10 a quaternary ammonium salt substituted thereon, alkoxycarbonyl, aryloxy carbonyl, alkylcarbonyloxy and arylcarbonyloxy, (O,O)-dioxyalkylene,

$-[O(CH_2)_w]_xX$ where x is 2 to 12, w is 2 or 3 and X comprises halo or a quaternary ammonium salt, thiophene, 15 pyridine, pyrrole, thiazole, imidazole, pyrazole, or furan.

The aryl group of R^5 or R^6 is preferably phenyl, phenylene, or benzene triyl, i.e., may be unsubstituted, mono-substituted, or di-substituted. Among the species which may constitute the substituents on the aryl ring of R^5 or R^6 are 20 fluoro, chloro, bromo, methoxy, ethoxy, isopropoxy, trimethylammonium (preferably with an iodide or chloride counterion), methoxycarbonyl, ethoxycarbonyl, formyl, acetyl, propanoyl, (N)-hexyldimethylammonium, hexylenetrimethylammonium, tri(oxyethylene)iodide, and 25 tetra(oxyethylene)trimethyl-ammonium iodide, each substituted at the p-position, the m-position, or both of the aryl ring. Other substituents that can be present on a phenylene, benzene triyl or other aromatic ring include 3,4-dioxymethylene (5-membered ring) and 3,4-dioxyethylene (6- 30 membered ring). Among compounds which have been or can be demonstrated to have desirable ileal bile acid transport inhibiting properties are those in which R^5 or R^6 is selected from phenyl, p-fluorophenyl, m-fluorophenyl, p-hydroxyphenyl, m-hydroxyphenyl, p-methoxyphenyl, m-methoxyphenyl, p-N,N-dimethylaminophenyl, m-N,N-

SRL 6071
(C-3021/2)

231

dimethylaminophenyl, I⁻ p-(CH₃)₃-N⁺-phenyl, I⁻ m-(CH₃)₃-N⁺-phenyl, I⁻ m-(CH₃)₃-N⁺-CH₂CH₂-(OCH₂CH₂)₂-O-phenyl, I⁻ p-(CH₃)₃-N⁺-CH₂CH₂-(OCH₂CH₂)₂-O-phenyl, I⁻ m-(N,N-dimethylpiperazinium)-(N')-CH₂-(OCH₂CH₂)₂-O-phenyl, 3-methoxy-4-fluorophenyl, 5 thienyl-2-yl, 5-cholorothiienyl-2-yl, 3,4-difluorophenyl, I⁻ p-(N,N-dimethylpiperazinium)-(N')-CH₂-(OCH₂CH₂)₂-O-phenyl, 3-fluoro-4-methoxyphenyl, -4-pyridinyl, 2-pyridinyl, 3-pyridinyl, N-methyl-4-pyridinium, I⁻ N-methyl-3-pyridinium, 3,4-dioxyethylenephenyl, and p-10 methoxycarbonylphenyl. Preferred compounds include 3-ethyl-3-butyl and 3-butyl-3-butyl compounds having each of the above preferred R⁵ substituents in combination with the R^x substituents shown in Table 1. It is particularly preferred that one but not both of R⁵ and R⁶ is hydrogen.

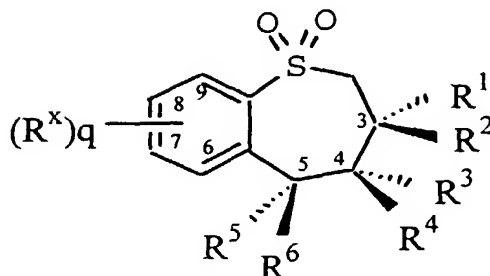
15 It is especially preferred that R⁴ and R⁶ be hydrogen, that R³ and R⁵ not be hydrogen, and that R³ and R⁵ be oriented in the same direction relative to the plane of the molecule, i.e., both in α- or both in β-configuration. It is further preferred that, where R² is butyl and R¹ is ethyl, 20 then R¹ has the same orientation relative to the plane of the molecule as R³ and R⁵.

Set forth in Table 1A are lists of species of R¹/R², R⁵/R⁶ and R^x.

SRL 6071
(C-3021/2)

232

Table 1A: Alternative R Groups



| R ¹ , R ² | R ³ , R ⁴ | R ⁵ | (R ⁵) _q |
|---|---------------------------------|---|--|
| ethyl | HO- | Ph- | 7-methyl |
| n-propyl | H- | p-F-Ph- | 7-ethyl |
| n-butyl | | m-F-Ph- | 7-iso-propyl |
| n-pentyl | | p-CH ₃ O-Ph- | 7-tert-butyl |
| n-hexyl | | p-CH ₃ O-Ph- | 7-OH |
| iso-propyl | | m-CH ₃ O-Ph- | 7-OCH ₃ |
| iso-butyl | | p-(CH ₃) ₂ N-Ph- | 7-O(iso-propyl) |
| iso-pentyl | | m-(CH ₃) ₂ N-Ph- | 7-SCH ₃ |
| CH ₂ C(=O)C ₂ H ₅ | | I ⁻ , p-(CH ₃) ₃ N ⁺ -Ph- | 7-SOCH ₃ |
| CH ₂ OC ₂ H ₅ | | I ⁻ , m-(CH ₃) ₃ N ⁺ -Ph- | 7-SO ₂ CH ₃ |
| CH ₂ CH(OH)C ₂ H ₅ | | I ⁻ , p-(CH ₃) ₃ N ⁺ -CH ₂ CH ₂ - | 7-SCH ₂ CH ₃ |
| CH ₂ O-(4-picoline) | | (OCH ₂ CH ₂) ₂ -O-Ph- | 7-NH ₂ |
| | | I ⁻ , m-(CH ₃) ₃ N ⁺ -CH ₂ CH ₂ - | 7-NHOH |
| | | (OCH ₂ CH ₂) ₂ -O-Ph- | 7-NHCH ₃ |
| | | I ⁻ , p-(N,N-dimethylpiperazine)-(N')-CH ₂ -(OCH ₂ CH ₂) ₂ -O-Ph- | 7-N(CH ₃) ₂ |
| | | I ⁻ , m-(N,N-dimethylpiperazine)-(N')-CH ₂ -(OCH ₂ CH ₂) ₂ -O-Ph- | 7-N ⁺ (CH ₃) ₃ , I ⁻ |
| | | m-F, p-CH ₃ O-Ph- | 7-NHC(=O)CH ₃ |
| | | 3,4-dioxymethylene-Ph | 7-N(CH ₂ CH ₃) ₂ |
| | | m-CH ₃ O-, p-F-Ph- | 7-NMeCH ₂ CO ₂ H |
| | | 4-pyridine | 7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻ |
| | | N-methyl-4-pyridinium, I ⁻ | 7-(N)-morpholine |
| | | 3-pyridine | 7-(N)-azetidine |
| | | N-methyl-3-pyridinium, I ⁻ | 7-(N)-N-methylazetidinium, I ⁻ |
| | | 2-pyridine | 7-(N)-pyrrolidine |
| | | p-CH ₃ O ₂ C-Ph- | 7-(N)-N-methylpyrrolidinium, I ⁻ |
| | | thienyl-2-yl | 7-(N)-N-methylmorpholinium, I ⁻ |
| | | 5-Cl-thienyl-2-yl | 7-(N)-N'-methylpiperazine |
| | | | 7-(N)-N'-dimethylpiperazinium, I ⁻ |
| | | | 7-NH-CBZ |
| | | | 7-NHC(O)C ₅ H ₁₁ |
| | | | 7-NHC(O)CH ₂ Br |
| | | | 7-NH-C(NH)NH ₂ |
| | | | 7-(2)-thiophene |

continued next page...

SRL 6071
(C-3021/2)

233

8-methyl
8-ethyl
8-iso-propyl
8-tert-butyl
8-OH
8-OCH₃
8-O(iso-propyl)
8-SCH₃
8-SOCH₃
8-SO₂CH₃
8-SCH₂CH₃
8-NH₂
8-NHOH
8-NHCH₃
8-N(CH₃)₂
8-N⁺(CH₃)₃, I⁻
8-NHC(=O)CH₃
8-N(CH₂CH₃)₂
8-NMeCH₂CO₂H
8-N⁺(Me)₂CH₂CO₂H, I⁻
8-(N)-morpholine
8-(N)-azetidine
8-(N)-N-methylazetidinium,
I⁻
8-(N)-pyrrolidine
8-(N)-N-methyl-
pyrrolidinium, I⁻
8-(N)-N-methyl-
morpholinium, I⁻
8-(N)-N'-methylpiperazine
8-(N)-N'-
dimethylpiperazinium,
I⁻
8-NH-CBZ
8-NHC(O)C₅H₁₁
8-NHC(O)CH₂Br
8-NH-C(NH)NH₂
8-(2)-thiophene

continued next page...

SRL 6071
(C-3021/2)

234

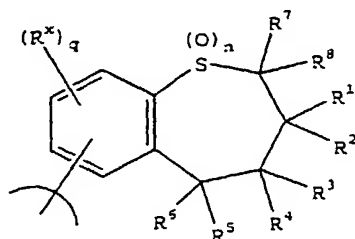
9-methyl
9-ethyl
9-iso-propyl
9-tert-butyl
9-OH
9-OCH₃
9-O(iso-propyl)
9-SCH₃
9-SOCH₃
9-SO₂CH₃
9-SCH₂CH₃
9-NH₂
9-NHOH
9-NHCH₃
9-N(CH₃)₂
9-N⁺(CH₃)₃, I⁻
9-NHC(=O)CH₃
9-N(CH₂CH₃)₂
9-NMeCH₂CO₂H
9-N⁺(Me)₂CH₂CO₂H, I⁻
9-(N)-morpholine
9-(N)-azetidine
9-(N)-N-methylazetidinium,
I⁻
9-(N)-pyrrolidine
9-(N)-N-methyl-
pyrrolidinium, I⁻
9-(N)-N-methyl-
morpholinium, I⁻
9-(N)-N'-methylpiperazine
9-(N)-N'-
dimethylpiperazinium,
I⁻
9-NH-CBZ
9-NHC(O)C₅H₁₁
9-NHC(O)CH₂Br
9-NH-C(NH)NH₂
9-(2)-thiophene

7-OCH₃, 8-OCH₃
7-SCH₃, 8-OCH₃
7-SCH₃, 8-SCH₃
6-OCH₃, 7-OCH₃, 8-OCH₃

SRL 6071
(C-3021/2)

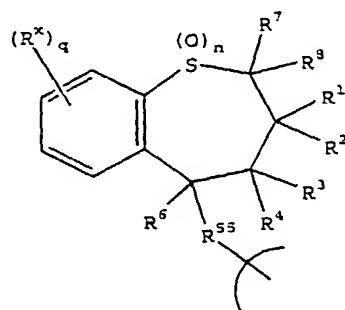
235

Further preferred compounds of the present invention comprise a core structure having two or more pharmaceutically active benzothiepine structures as described above, covalently bonded to the core moiety via functional linkages. Such active benzothiepine structures preferably comprise:



(Formula DIV)

or:



(Formula DIVA)

where R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , X , q and n are as defined above, and R^{55} is either a covalent bond or arylene.

SRL 6071
(C-3021/2)

236

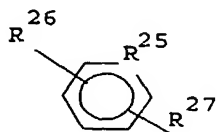
The core moiety can comprise alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide, polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, and peptide polypeptide, can optionally have one or more carbon replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{R}^8$, PR^7 , $\text{P}^+\text{R}^7\text{R}^8$, phenylene, heterocycle, quaternary heterocycle, quaternary heteroaryl, or aryl, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $\text{NR}^{13}\text{R}^{14}$, SR^{13} , $\text{S}(\text{O})\text{R}^{13}$, SO_2R^{13} , SO_3R^{13} , $\text{NR}^{13}\text{OR}^{14}$, $\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$, NO_2 , CO_2R^{13} , CN, OM, SO_2OM , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{OM}$, COR^{13} , $\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$, $\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$, $\text{P}(\text{OR}^{13})\text{OR}^{14}$, $\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$, and $\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$; wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , NR^7R^8 , SR^7 , $\text{S}(\text{O})\text{R}^7$, SO_2R^7 , SO_3R^7 , CO_2R^7 , CN, oxo, CONR^7R^8 , $\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $\text{P}(\text{O})\text{R}^7\text{R}^8$, $\text{P}^+\text{R}^7\text{R}^8\text{A}^-$, and $\text{P}(\text{O})(\text{OR}^7)\text{OR}^8$, and wherein said alkyl, alkenyl, alkynyl, polyalkyl,

SRL 6071
(C-3021/2)

237

polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $\text{N}^+\text{R}^7\text{R}^8\text{A}-$, S, SO, SO_2 , $\text{S}^+\text{R}^7\text{A}-$, PR^7 , $\text{P}(\text{O})\text{R}^7$, $\text{P}^+\text{R}^7\text{R}^8\text{A}-$, or phenylene.

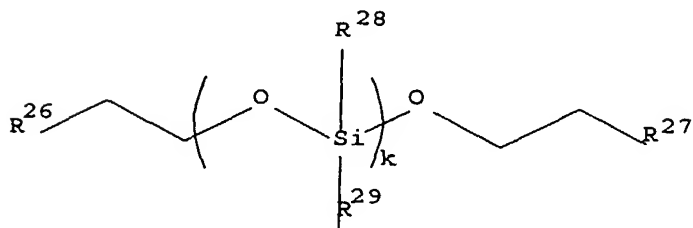
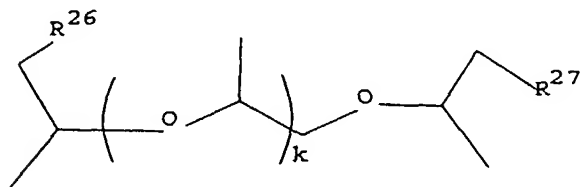
5 Exemplary core moieties include:



10



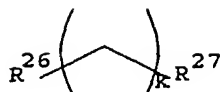
15



20

SRL 6071
(C-3021/2)

238

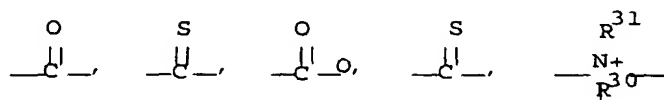


wherein:

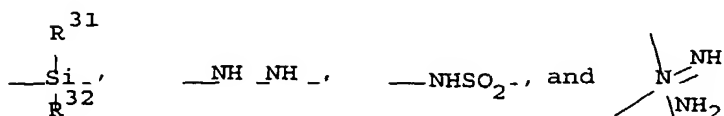
5 R^{25} is selected from the group consisting of C and N, and

R^{26} and R^{27} are independently selected from the group consisting of:

10



15



20 wherein R^{26} , R^{29} , R^{30} and R^{31} are independently selected from alkyl, alkenyl, alkylaryl, aryl, arylalkyl, cycloalkyl, heterocycle, and heterocycloalkyl,

A^- is a pharmaceutically acceptable anion, and $k = 1$ to 10.

25 In compounds of Formula DIV, R^{20} , R^{21} , R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII can be bonded at any of their 6-, 7-, 8-, or 9- positions to R^{19} . In compounds of Formula DIVA, it is preferred that

SRL 6071
(C-3021/2)

239

R^{55} comprises a phenylene moiety bonded at a m- or p-position thereof to R^{19} .

In another embodiment, a core moiety backbone, R^{19} , as discussed herein in Formulas DII and DIII can be multiply substituted with more than four pendant active benzothiepine units, i.e., R^{20} , R^{21} , R^{22} , and R^{23} as discussed above, through multiple functional groups within the core moiety backbone. The core moiety backbone unit, R^{19} , can comprise a single core moiety unit, multimers thereof, and multimeric mixtures of the different core moiety units discussed herein, i.e., alone or in combination. The number of individual core moiety backbone units can range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. The number of points of attachment of similar or different pendant active benzothiepine units within a single core moiety backbone unit can be in the range from about one to about 100, preferably about one to about 80, more preferably about one to about 50, and even more preferably about one to about 25. Such points of attachment can include bonds to C, S, O, N, or P within any of the groups encompassed by the definition of R^{19} .

The more preferred benzothiepine moieties comprising R^{20} , R^{21} , R^{22} and/or R^{23} conform to the preferred structures as outlined above for Formula I. The 3-carbon on each benzothiepine moiety can be achiral, and the substituents R^1 , R^2 , R^3 , R^4 , R^5 and R^x can be selected from the preferred groups and combinations of substituents as discussed above. The core structures can comprise, for example, poly(exyalkylene) or oligo(oxyalkylene), especially poly- or oligo(exyethylene) or poly- or oligo(oxypropylene).

SRL 6071
(C-3021/2)

240

Dosages, Formulations, and Routes of Administration

5 The ileal bile acid transport inhibitor compounds of the present invention can be administered for the prophylaxis and treatment of hyperlipidemic diseases or conditions by any means, preferably oral, that produce contact of these compounds with their site of action in the body, for example in the ileum of a mammal, e.g., a human.

10 For the prophylaxis or treatment of the conditions referred to above, the compounds of the present invention can be used as the compound *per se*.

15 Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible
20 include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic,
25 isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium
30 salts, alkali metal salts such as sodium and potassium salts, and alkaline earth salts such as magnesium and calcium salts.

35 The anions of the definition of A⁻ in the present invention are, of course, also required to be pharmaceutically acceptable and are also selected from

SRL 6071
(C-3021/2)

241

the above list.

5 The compounds of the present invention can be
presented with an acceptable carrier in the form of a
pharmaceutical composition. The carrier must, of
course, be acceptable in the sense of being compatible
with the other ingredients of the composition and must
not be deleterious to the recipient. The carrier can
be a solid or a liquid, or both, and is preferably
formulated with the compound as a unit-dose
10 composition, for example, a tablet, which can contain
from 0.05% to 95% by weight of the active compound.
Other pharmacologically active substances can also be
present, including other compounds of the present
invention. The pharmaceutical compositions of the
15 invention can be prepared by any of the well known
techniques of pharmacy, consisting essentially of
admixing the components.

20 These compounds can be administered by any
conventional means available for use in conjunction
with pharmaceuticals, either as individual therapeutic
compounds or as a combination of therapeutic compounds.

25 The amount of compound which is required to
achieve the desired biological effect will, of course,
depend on a number of factors such as the specific
compound chosen, the use for which it is intended, the
mode of administration, and the clinical condition of
the recipient.

30 In general, a daily dose can be in the range of
from about 0.3 to about 100 mg/kg bodyweight/day,
preferably from about 1 mg to about 50 mg/kg
bodyweight/day, more preferably from about 3 to about
10 mg/kg bodyweight/day. This total daily dose can be
administered to the patient in a single dose, or in
35 proportionate multiple subdoses. Subdoses can be

SRL 6071
(C-3021/2)

242

administered 2 to 6 times per day. Doses can be in sustained release form effective to obtain desired results.

Orally administrable unit dose formulations, such as tablets or capsules, can contain, for example, from about 0.1 to about 100 mg of benzothiepine compound, preferably about 1 to about 75 mg of compound, more preferably from about 10 to about 50 mg of compound. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiepine ion derived from the salt.

Oral delivery of an ileal bile acid transport inhibitor of the present invention can include formulations, as are well known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. These include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (the ileum) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

When administered intravenously, the dose can, for

SRL 6071
(C-3021/2)

243

example, be in the range of from about 0.1 mg/kg body weight to about 1.0 mg/kg body weight, preferably from about 0.25 mg/kg body weight to about 0.75 mg/kg body weight, more preferably from about 0.4 mg/kg body weight to about 0.6 mg/kg body weight. This dose can be conveniently administered as an infusion of from about 10 ng/kg body weight to about 100 ng/kg body weight per minute. Infusion fluids suitable for this purpose can contain, for example, from about 0.1 ng to about 10 mg, preferably from about 1 ng to about 10 mg per milliliter. Unit doses can contain, for example, from about 1 mg to about 10 g of the compound of the present invention. Thus, ampoules for injection can contain, for example, from about 1 mg to about 100 mg.

Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g., sublingual), and parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound which is being used. In most cases, the preferred route of administration is oral.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound(s) and the carrier (which can

SRL 6071
(C-3021/2)

244

constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if
5 necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the
10 compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with
15 an inert liquid diluent.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or
20 tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration conveniently comprise sterile
25 aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such
30 preparations can conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of a compound
35 disclosed herein.

SRL 6071
(C-3021/2)

245

Pharmaceutical compositions suitable for rectal administration are preferably presented as unit-dose suppositories. These can be prepared by admixing a compound of the present invention with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which can be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain a compound of the present invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the compound can be delivered from the patch by electrotransport or iontophoresis, for example, as described in Pharmaceutical Research, 3(6), 318 (1986).

In any case, the amount of active ingredient that can be combined with carrier materials to produce a single dosage form to be administered will vary depending upon the host treated and the particular mode of administration.

The solid dosage forms for oral administration

SRL 6071
(C-3021/2)

246

including capsules, tablets, pills, powders, and granules noted above comprise one or more compounds of the present invention admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or setting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Pharmaceutically acceptable carriers encompass all the foregoing and the like.

SRL 6071
(C-3021/2)

247

Treatment Regimen

5 The dosage regimen to prevent, give relief from,
or ameliorate a disease condition having hyperlipemia
as an element of the disease, e.g., atherosclerosis, or
to protect against or treat further high cholesterol
plasma or blood levels with the compounds and/or
compositions of the present invention is selected in
accordance with a variety of factors. These include
10 the type, age, weight, sex, diet, and medical condition
of the patient, the severity of the disease, the route
of administration, pharmacological considerations such
as the activity, efficacy, pharmacokinetics and
toxicology profiles of the particular compound
15 employed, whether a drug delivery system is utilized,
and whether the compound is administered as part of a
drug combination. Thus, the dosage regimen actually
employed may vary widely and therefore deviate from the
preferred dosage regimen set forth above.

20 Initial treatment of a patient suffering from a
hyperlipidemic condition can begin with the dosages
indicated above. Treatment should generally be
continued as necessary over a period of several weeks
to several months or years until the hyperlipidemic
25 disease condition has been controlled or eliminated.
Patients undergoing treatment with the compounds or
compositions disclosed herein can be routinely
monitored by, for example, measuring serum cholesterol
levels by any of the methods well known in the art, to
30 determine the effectiveness of therapy. Continuous
analysis of such data permits modification of the
treatment regimen during therapy so that optimal
effective amounts of compounds of the present invention
are administered at any point in time, and so that the
35 duration of treatment can be determined as well. In

SRL 6071
(C-3021/2)

248

5 this way, the treatment regimen/dosing schedule can be
rationally modified over the course of therapy so that
the lowest amount of ileal bile acid transport
inhibitor of the present invention which exhibits
satisfactory effectiveness is administered, and so that
administration is continued only so long as is
necessary to successfully treat the hyperlipidemic
condition.

10 The following non-limiting examples serve to
illustrate various aspects of the present invention.

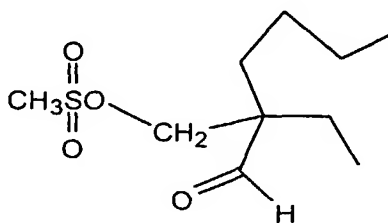
SRL 6071
(C-3021/2)

249

EXAMPLES OF SYNTHETIC PROCEDURES

Preparation 1

2-Ethyl-2-(mesyloxymethyl)hexanal (1)



5

1

To a cold (10 °C) solution of 12.6 g (0.11 mole) of
methanesulfonyl chloride and 10.3 g (0.13 mole) of
triethylamine was added dropwise 15.8 g of 2-ethyl-2-
10 (hydroxymethyl)hexanal, prepared according to the
procedure described in Chem. Ber. **98**, 728-734 (1965),
while maintaining the reaction temperature below 30 °C.
The reaction mixture was stirred at room temperature
for 18 h, quenched with dilute HCl and extracted with
15 methylene chloride. The methylene chloride extract was
dried over MgSO₄ and concentrated in vacuo to give 24.4
g of brown oil.

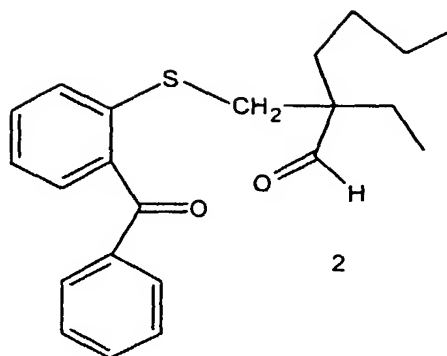
Preparation 2

20

2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

SRL 6071
(C-3021/2)

250



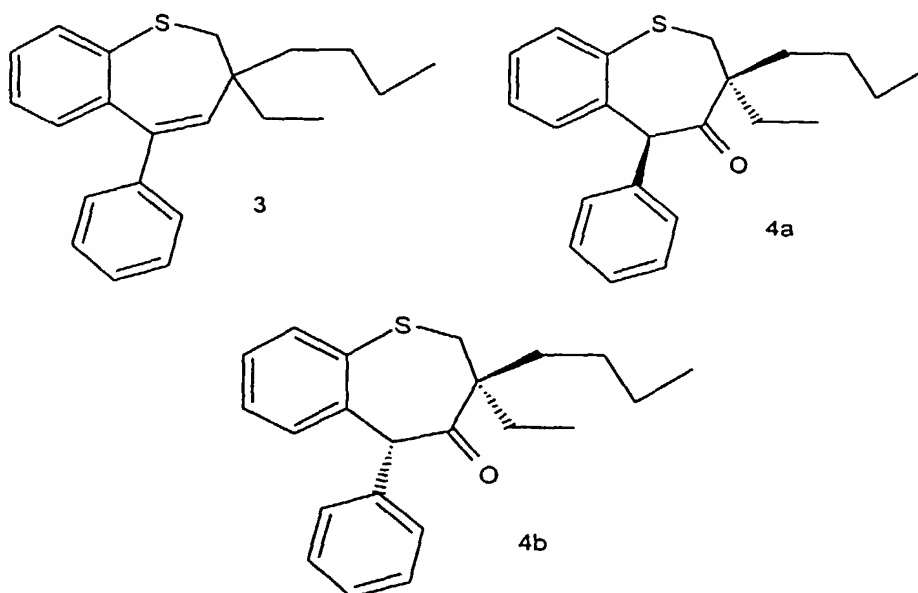
A mixture of 31 g (0.144 mol) of 2-mercaptobenzophenone, prepared according to the
5 procedure described in WO 93/16055, 24.4 g (0.1 mole) of 2-ethyl-2-(mesyloxymethyl)-hexanal (1), 14.8 g
(0.146 mole) of triethylamine, and 80 mL of 2-methoxyethyl ether was held at reflux for 24 h. The
reaction mixture was poured into 3N HCl and extracted
10 with 300 mL of methylene chloride. The methylene chloride layer was washed with 300 mL of 10% NaOH,
dried over MgSO₄ and concentrated in vacuo to remove 2-methoxyethyl ether. The residue was purified by HPLC
(10% EtOAc-hexane) to give 20.5 g (58%) of 2 as an oil.
15

SRL 6071
(C-3021/2)

251

Example 1

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine (3),
cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-
(5*H*) 4-one (4a) and *trans*-3-Butyl-3-ethyl-5-phenyl-2,3-
5 dihydro-benzothiepin-(5*H*) 4-one (4b)



10 A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g
(0.047 mole) of TiCl_3 and 80 mL of anhydrous ethylene
glycol dimethyl ether (DME) was held at reflux for 2 h.
The reaction mixture was cooled to 5 °C. To the
reaction mixture was added dropwise a solution of 3.54
15 g (0.01 mole) of 2 in 30 mL of DME in 40 min. The
reaction mixture was stirred at room temperature for 16
h and then was held at reflux for 2 h and cooled before
being poured into brine. The organic was extract into
methylene chloride. The methylene chloride extract was
20 dried over MgSO_4 and concentrated in vacuo. The residue
was purified by HPLC (hexane) to give 1.7 g (43%) of 3
as an oil in the first fraction. The second fraction

SRL 6071
(C-3021/2)

252

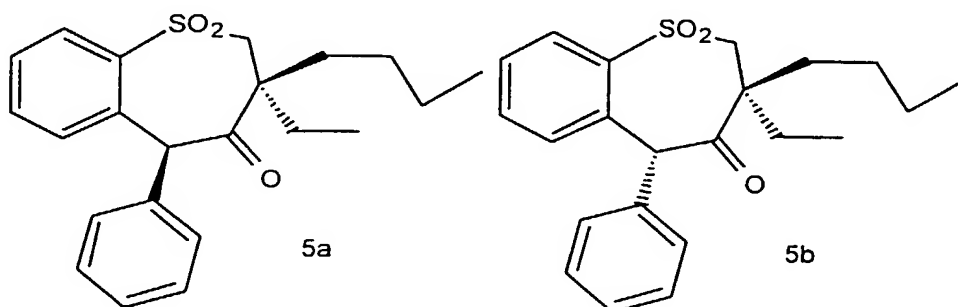
was discarded and the third fraction was further purified by HPLC (hexane) to give 0.07 g (2%) of **4a** in the earlier fraction and 0.1 g (3%) of **4b** in the later fraction.

5

Example 2

cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5*H*) 4-one-1,1-dioxide (**5a**) and *trans*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5*H*) 4-one-1,1-dioxide (**5b**)

10



To a solution of 1.2 g (3.5 mmole) of 50-60% MCPBA in 20 mL of methylene chloride was added 0.59 g (1.75 mmole) of a mixture of **4a** and **4b** in 10 mL of methylene chloride. The reaction mixture was stirred for 20 h. An additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added and the reaction mixture was stirred for an additional 3 h then was triturated with 50 mL of 10% NaOH. The insoluble solid was filtered. The methylene chloride layer of the filtrate was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residual syrup was purified by HPLC (5% EtOAc-hexane) to give 0.2 g (30%) of **5a** as an oil in the first fraction and 0.17 g (26%) of **5b** as an oil in the second fraction.

15

20

25

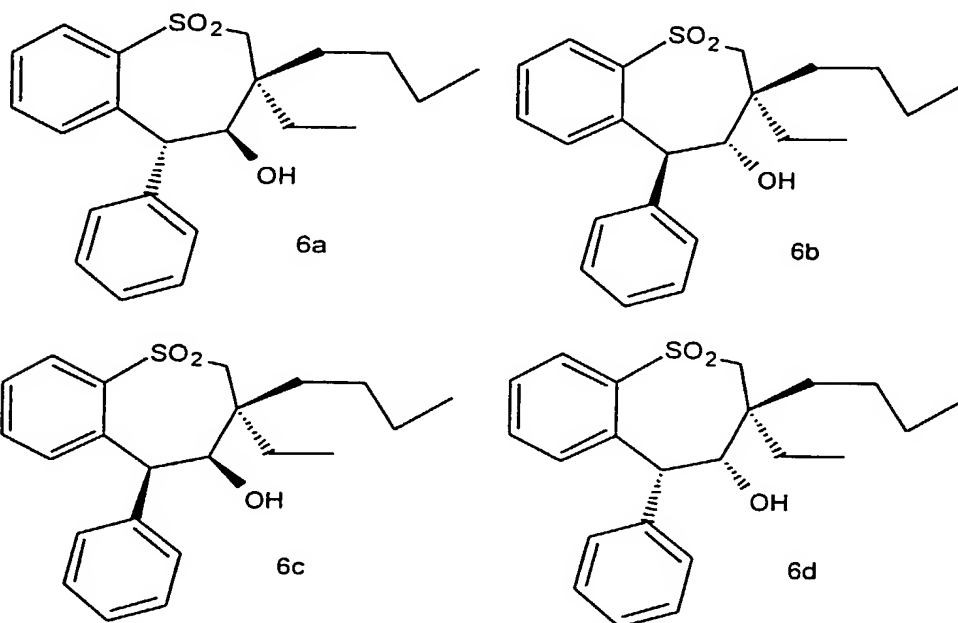
Example 3

(3 α ,4 α ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-

SRL 6071
(C-3021/2)

253

5 tetrahydrobenzothiepine-1,1-dioxide (6a), (3 α ,4 β ,5 α) 3-
Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-
benzothiepine-1,1-dioxide (6b), (3 α ,4 α ,5 α) 3-Butyl-3-
ethyl-4-hydroxy-5-phenyl-2,3,4,5-
tetrahydrobenzothiepine-1,1-dioxide (6c), and
(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-
tetrahydrobenzothiepine-1,1-dioxide (6d)



10 **A. Reduction of 5a and 5b with Sodium Borohydride**

To a solution of 0.22 g (0.59 mmole) of **5b** in 10 mL of
ethanol was added 0.24 g (6.4 mmole) of sodium
15 borohydride. The reaction mixture was stirred at room
temperature for 18 h and concentrated in vacuo to
remove ethanol. The residue was triturated with water
and extracted with methylene chloride. The methylene
chloride extract was dried over MgSO₄ and concentrated
20 in vacuo to give 0.2 g of syrup. In a separate
experiment, 0.45 g of **5a** was treated with 0.44 g of

SRL 6071
(C-3021/2)

254

sodium borohydride in 10 mL of ethanol and was worked up as described above to give 0.5 g of syrup which was identical to the 0.2 g of syrup obtained above. These two materials were combined and purified by HPLC using 10% EtOAc-hexane as eluant. The first fraction was 0.18 g (27%) of **6a** as a syrup. The second fraction was 0.2 g (30%) of **6b** also as a syrup. The column was then eluted with 20% EtOAc-hexane to give 0.077 g (11%) of **6c** in the third fraction as a solid. Recrystallization from hexane gave a solid, mp 179-181 °C. Finally, the column was eluted with 30% EtOAc-hexane to give 0.08 g (12%) of **6d** in the fourth fraction as a solid. Recrystallization from hexane gave a solid, mp 160-161 °C.

B. Conversion of **6a** to **6c** and **6d** with NaOH and PTC

To a solution of 0.29 g (0.73 mmole) of **6a** in 10 mL CH₂Cl₂, was added 9 g of 40% NaOH. The reaction mixture was stirred for 0.5 h at room temperature and was added one drop of Aliquat-336 (methyltricaprylammonium chloride) phase transfer catalyst (PTC). The mixture was stirred for 0.5 h at room temperature before being treated with 25 mL of ice-crystals then was extracted with CH₂Cl₂ (3x10 ml), dried over MgSO₄ and concentrated in vacuo to recover 0.17 g of a colorless film. The components of this mixture were separated using an HPLC and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2-(2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the first fraction, 30.9 mg (11%) of **6c** in the second fraction and 90.0 mg (31%) of **6d** in the third fraction.

SRL 6071
(C-3021/2)

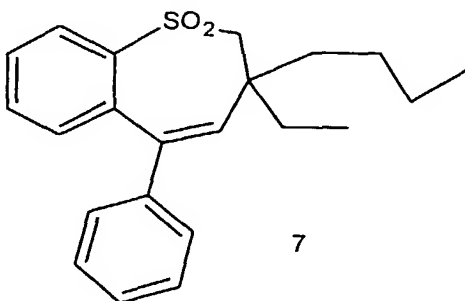
255

Oxidation of 6a to 5b

To a solution of 0.20 g (0.52 mmole) of **6a** in 5 mL of CH_2Cl_2 was added 0.23 g (1.0 mmole) of pyridinium chlorochromate. The reaction mixture was stirred for 2 h then was treated with additional 0.23 g of pyridinium chlorochromate and stirred overnight. The dark reaction mixture was poured into a ceramic filterfrit containing silica gel and was eluted with CH_2Cl_2 . The filtrate was concentrated in vacuo to recover 167 mg (87%) of **5b** as a colorless oil.

Example 4

3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-dioxide (7)



15

To a solution of 5.13 g (15.9 mmole) of **3** in 50 mL of CH_2Cl_2 was added 10 g (31.9 mmole) of 50-60% MCPBA (m-chloroperoxybenzoic acid) portionwise causing a mild reflux and formation of a white solid. The reaction mixture was allowed to stir overnight under N_2 and was triturated with 25 mL of water followed by 50 mL of 10% NaOH solution. The organic was extracted into CH_2Cl_2 (4x20 mL). The CH_2Cl_2 extract was dried over MgSO_4 and evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

25

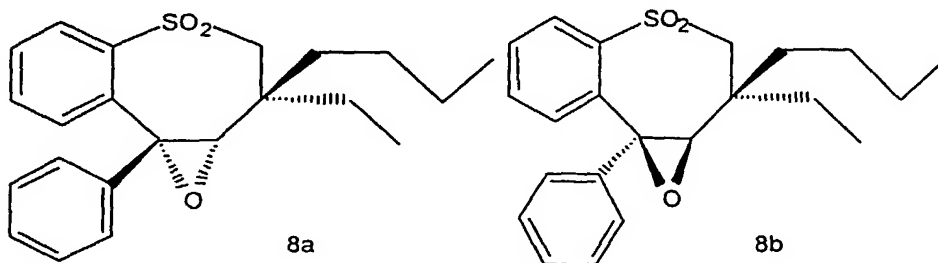
Example 5

SRL 6071
(C-3021/2)

256

(1 α ,2 β ,8 $\beta\alpha$) 2-Butyl-2-ethyl-8 β -phenyl-1 α ,2,3,8 β -
tetrahydro-benzothiepine[4,5-*b*]oxirene-4,4-dioxide (8a)

(1 α ,2 α ,8 $\beta\alpha$) 2-Butyl-2-ethyl-8 β -phenyl-1 α ,2,3,8 β -
tetrahydro-benzothiepine[4,5-*b*]oxirene-4,4-dioxide (8b)



5
10
15
20
To 1.3 g (4.03 mmole) of **3** in 25 mL of CHCl₃, was added
portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a
mild exotherm. The reaction mixture was stirred under
N₂ overnight and was then held at reflux for 3 h. The
insoluble white slurry was filtered. The filtrate was
extracted with 10% potassium carbonate (3x50 mL), once
with brine, dried over MgSO₄, and concentrated in vacuo
to give 1.37 g of a light yellow oil. Purification by
HPLC gave 0.65 g of crystalline product. This product
is a mixture of two isomers. Trituration of this
crystalline product in hexane recovered 141.7 mg (10%)
of a white crystalline product. This isomer was
characterized by NMR and mass spectra to be the
(1 α ,2 β ,8 $\beta\alpha$) isomer **8a**. The hexane filtrate was
concentrated in vacuo to give 206 mg of white film
which is a mixture of 30% **8a** and 70% **8b** by ¹H NMR.

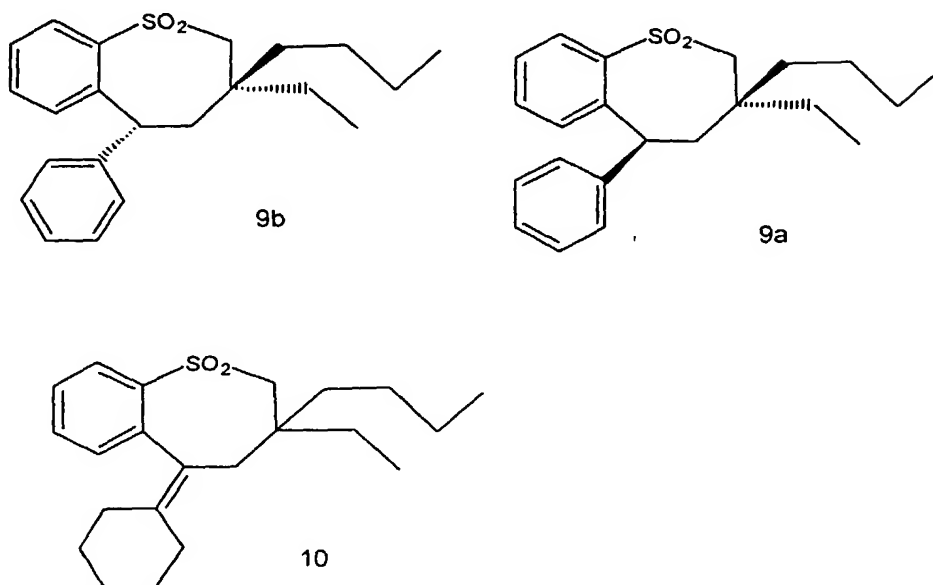
Example 6

25
cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-
benzothiepine-1,1-dioxide (**9a**), trans-3-Butyl-3-ethyl-
5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
(**9b**), and 3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidine-
2,3,4,5-

SRL 6071
(C-3021/2)

257

tetrahydrobenzothiepine-1,1-dioxide (10)



A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of **8a** and **8b** was dissolved in 15 ml MeOH in a 3 oz. Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C catalyst. This mixture was hydrogenated at 70 psi H₂ for 5 h and filtered. The filtrate was evaporated to dryness in vacuo to recover 0.117 g of a colorless oil. This material was purified by HPLC eluting with EtOAc-hexane. The first fraction was 4.2 mg (3%) of **9b**. The second fraction, 5.0 mg (4%), was a 50/50 mixture of **9a** and **9b**. The third fraction was 8.8 mg (6%) of **6a**. The fourth fraction was 25.5 mg (18%) of **6b**. The fifth fraction was 9.6 mg (7%) of a mixture of **6b** and a product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide based on mass spectrum. The sixth fraction was 7.5 mg (5%) of a mixture of **6d** and one of the isomers of **10**, **10a**.

Example 7

SRL 6071
(C-3021/2)

258

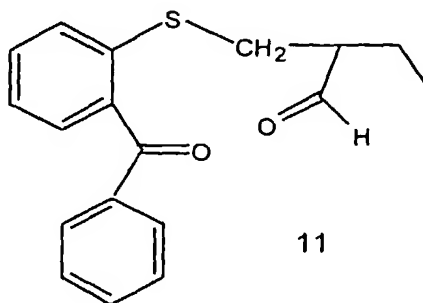
5 In another experiment, a product (3.7 g) from
epoxidation of **3** with excess MCPBA in refluxing CHCl₃
under air was hydrogenated in 100 mL of methanol using
1 g of 10% Pd/C catalyst and 70 psi hydrogen. The
product was purified by HPLC to give 0.9 g (25%) of **9b**,
0.45 g (13%) of **9a**, 0.27 g (7%) of **6a**, 0.51 g (14%) of
6b, 0.02 g (1%) of **6c**, 0.06 g (2%) of one isomer of **10**,
10a and 0.03 g (1%) of another isomer of **10**, **10b**.

SRL 6071
(C-3021/2)

259

Example 8

2-((2-Benzoylphenylthio)methyl)butyraldehyde (11)



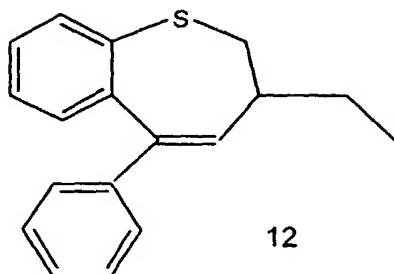
5 To an ice bath cooled solution of 9.76 g (0.116 mole)
of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g
(0.116 mole) of 2-mercaptobenzophenone in 40 mL of THF
followed by 13 g (0.128 mole) of triethylamine. The
reaction mixture was stirred at room temperature for 3
10 days , diluted with ether, and was washed successively
with dilute HCl, brine, and 1 M potassium carbonate.
The ether layer was dried over MgSO₄ and concentrated
in vacuo. The residue was purified by HPLC (10% EtOAc-
hexane) to give 22 g (64%) of 11 in the second
15 fraction. An attempt to further purify this material
by kugelrohr distillation at 0.5 torr (160-190 °C) gave
a fraction (12.2 g) which contained starting material
indicating a reversed reaction during distillation.
This material was dissolved in ether (100 mL) and was
20 washed with 50 mL of 1 M potassium carbonate three
times to give 6.0 g of a syrup which was purified by
HPLC (10% EtOAc-hexane) to give 5.6 g of pure 11.

Example 9

25 **3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine (12)**

SRL 6071
(C-3021/2)

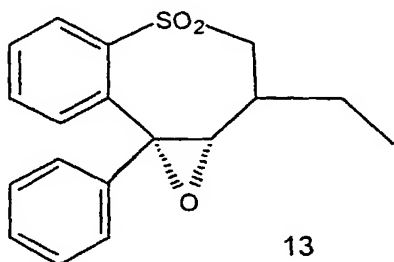
260



To a mixture of 2.61 g (0.04 mole) of zinc dust and 60 mL of DME was added 7.5 g (0.048 mole) of TiCl_3 . The reaction mixture was held at reflux for 2 h. A solution of 2.98 g (0.01 mole) of **11** was added dropwise in 1 h. The reaction mixture was held at reflux for 18 h, cooled and poured into water. The organic was extracted into ether. The ether layer was washed with brine and filtered through Celite. The filtrate was dried over MgSO_4 and concentrated. The residual oil (2.5 g) was purified by HPLC to give 2.06 g (77%) of **12** as an oil in the second fraction.

Example 10

(1a α ,2 α ,8b α) 2-Ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepine-[4,5-b]oxirene-4,4-dioxide (**13**)



To a solution of 1.5 g (5.64 mmole) of **12** in 25 ml of CHCl_3 was added 6.8 g (19.4 mmole) of 50-60% MCPB portionwise causing an exotherm and formation of a white solid. The mixture was stirred at room temperature

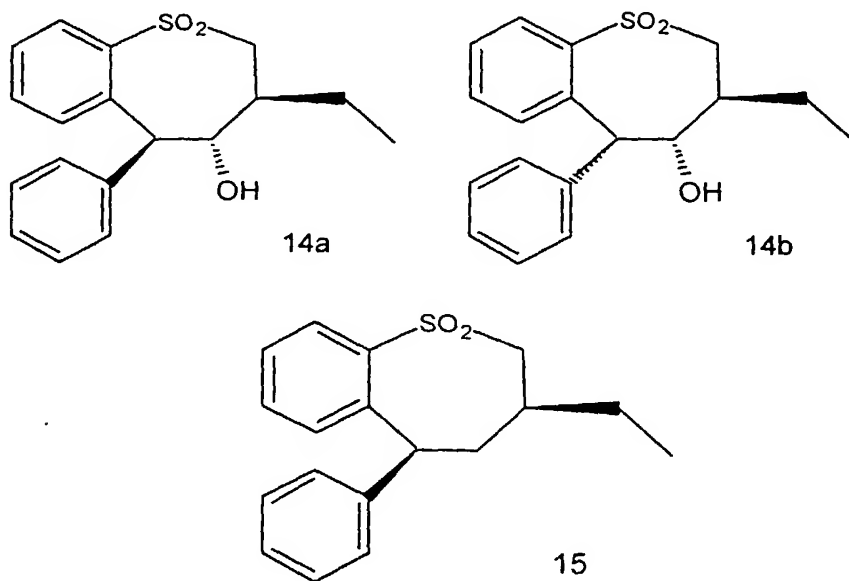
SRL 6071
(C-3021/2)

261

overnight diluted with 100 ml methylene chloride and washed successively with 10% K_2CO_3 (4x50 ml), water (twice with 25 ml) and brine. The organic layer was then dried over $MgSO_4$ and evaporated to dryness to recover 1.47 g of an off white solid. 1H NMR indicated that only one isomer is present. This solid was slurried in 200 ml of warm Et_2O and filtered to give 0.82 g (46%) of **13** as a white solid, mp 185-186.5 $^{\circ}C$.

Example 11

(3 α ,4 β ,5 α)- 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (**14a**), (3 α ,4 β ,5 β) 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**14b**), and cis-3-Ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (**15**)



A mixture of 0.5 g (1.6 mole) of **13**, 50 ml of acetic acid and 0.5 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 4 h. The crude reaction slurry

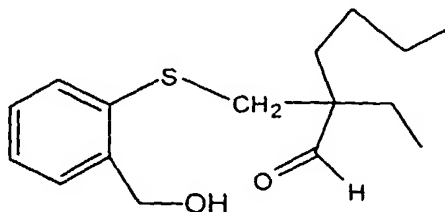
SRL 6071
(C-3021/2)

262

was filtered and the filtrate was stirred with 150 ml of a saturated NaHCO₃ solution followed by 89 g of NaHCO₃ powder portionwise to neutralize the rest of acetic acid. The mixture was extracted with methylene chloride (4x25 ml), then the organic layer was dried over MgSO₄ and concentrated in vacuo to give 0.44 g (87%) of a voluminous white solid which was purified by HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of **15** in the first fraction, 272 mg (54%) of **14a** as a solid, mp 142-143.5 °C, in the second fraction, and 35 mg (7%) of impure **14b** in the third fraction.

Example 12

2-Ethyl-2-((2-Hydroxymethylphenyl)thiomethyl)hexenal (16)



16

A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl alcohol, 6.4 g (0.032 mole) of **1**, 3.6 g (0.036 mole) of triethylamine and 25 mL of 2-methoxyethyl ether was held at reflux for 7 h. Additional 1.1 g of mercaptobenzyl alcohol and 0.72 g of triethylamine was added to the reaction mixture and the mixture was held at reflux for additional 16 h. The reaction mixture was cooled and poured into 6N HCl and extracted with methylene chloride. The methylene chloride extract was washed twice with 10% NaOH, dried over MgSO₄ and concentrated in vacuo to give 9.6 g of residue. Purification by HPLC (20% EtOAc-hexane) gave 3.7 g

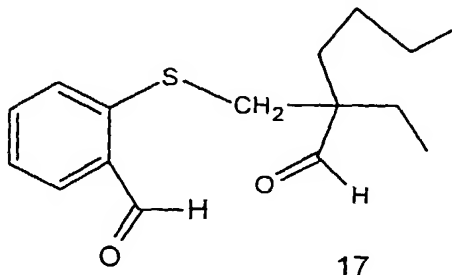
SRL 6071
(C-3021/2)

263

(41%) of **16** as an oil.

Example 13

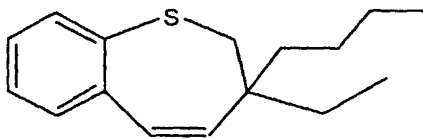
2-Ethyl-2-((2-formylphenyl)thiomethyl)hexenal (17)



5 A mixture of 3.7 g of **16**, 5.6 g (0.026 mole) of
pyridinium chlorochromate, 2 g of Celite and 30 mL of
methylene chloride was stirred for 18 h and filtered
10 through a bed of silica gel. The silica gel was eluted
with methylene chloride. The combined methylene
chloride eluant was purified by HPLC (20% ETOAc-hexane)
to give 2.4 g (66%) of an oil.

Example 14

15 **3-Butyl-3-ethyl-2,3-dihydrobenzothiepine (18)**



20 A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g
(0.047 mole) of TiCl_3 , and 50 mL of DME was held at
reflux for 2 h and cooled to room temperature. To this
mixture was added 2.4 g (8.6 mmole) of **17** in 20 mL of
DME in 10 min. The reaction mixture was stirred at room
temperature for 2 h and held at reflux for 1 h then was
let standing at room temperature over weekend. The
reaction mixture was poured into dilute HCl and was

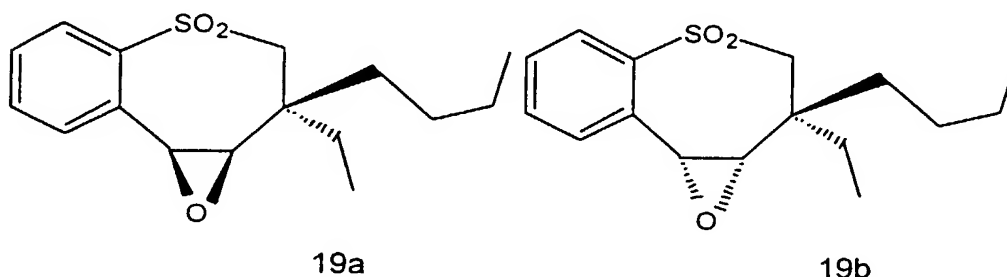
SRL 6071
(C-3021/2)

264

stirred with methylene chloride. The methylene
chloride-water mixture was filtered through Celite. The
methylene chloride layer was washed with brine, dried
over MgSO_4 , and concentrated in vacuo to give 3.0 g of
5 a residue. Purification by HPLC gave 0.41 g (20%) of **18**
as an oil in the early fraction.

Example 15

($1\alpha, 2\alpha, 8b\alpha$) 2-Butyl-2-ethyl-1a,2,3,8b-tetrahydro-
10 benzothiepino[4,5-b]oxirene-4,4-dioxide (**19a**) and
($1\alpha, 2\beta, 8b\alpha$) 2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-
tetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide
(**19b**)



15 To a solution of 0.4 g of **18** in 30 mL of methylene chloride was added 2.2 g (3.2 mmole) of 50-60% MCPBA. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was dissolved in 30 mL of CHCl_3 , and was held at reflux for 18 h under N_2 .
20 The reaction mixture was stirred with 100 mL of 10% NaOH and 5 g of sodium sulfite. The methylene chloride layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by HPLC (20% EtOAc-hexane) to give a third fraction which was
25 further purified by HPLC (10% EtOAc-hexane) to give 0.12 g of syrup in the first fraction. Recrystallization from hexane gave 0.08 g (17%) of **19a**, mp 89.5-105.5 °C. The mother liquor from the first

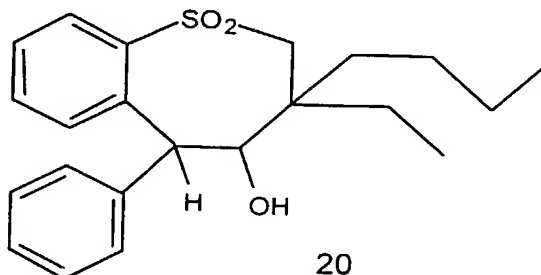
SRL 6071
(C-3021/2)

265

fraction was combined with the second fraction and was further purified by HPLC to give additional **19a** in the first fraction and 60 mg of **19b** in the second fraction. Crystallization from hexane gave 56 mg of a white solid.

Example 16

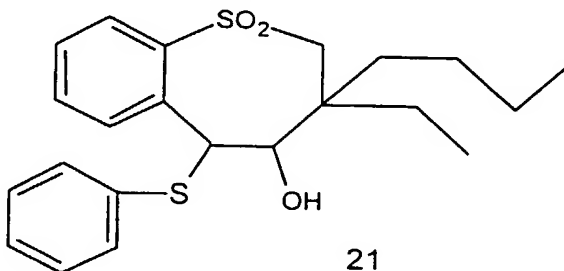
3-Butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (20)



This product was isolated along with **6b** from hydrogenation of a mixture of **8a** and **8b**.

Example 17

3-Butyl-3-ethyl-4-hydroxy-5-phenylthio-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (21)



A mixture of 25 mg (0.085 mmole) of **19b**, 0.27 g (2.7 mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium carbonate, and 4 mL of DMF was stirred at room temperature under N₂ for 19 h. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed

SRL 6071
(C-3021/2)

266

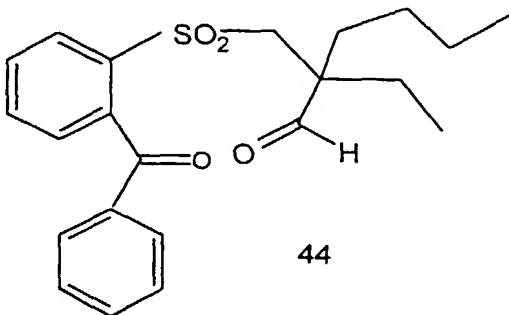
successively with 10% NaOH and brine, dried over MgSO_4 , and concentrated in vacuo to give 0.19 g of semisolid which contain substantial amounts of diphenyl disulfide. This material was purified by HPLC (5% EtOAc-hexane) to remove diphenyl disulfide in the first fraction. The column was then eluted with 20% EtOAc-hexane to give 17 mg of a first fraction, 4 mg of a second fraction and 11 mg of a third fraction which were three different isomers of 21, i.e. 21a, 21b, and 21c, respectively, by ^1H NMR and mass spectra.

Example 18

Alternative Synthesis of 6c and 6d

A. Preparation from 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)

Step 1. 2-((2-Benzoylphenylsulfonyl)methyl)-2-ethylhexanal (44)



To a solution of 9.0 g (0.025 mole) of compound 2 in 100 ml of methylene chloride was added 14.6 g (0.025 mol) of 50-60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h then was stirred with 200 ml of 1 M potassium carbonate and filtered through Celite. The methylene chloride layer was washed twice with 300 ml of 1 M potassium carbonate, once with 10% sodium hydroxide and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene

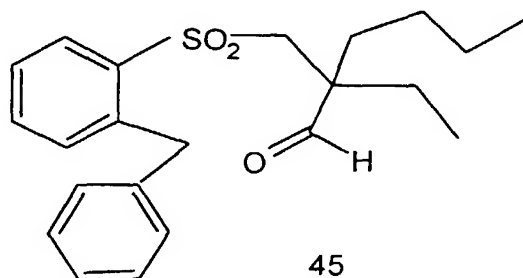
SRL 6071
(C-3021/2)

267

chloride solution was dried and concentrated in vacuo to give 9.2 g (95%) of semisolid. A portion (2.6 g) of this solid was purified by HPLC (10% ethyl acetate-hexane) to give 1.9 g of crystals, mp 135-136 °C

5

Step 2. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



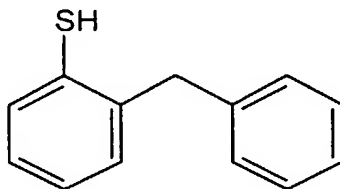
45

10 A solution of 50 g (0.13 mole) of crude **44** in 250 ml of methylene chloride was divided in two portions and charged to two Fisher-Porter bottles. To each bottle was charged 125 ml of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature
15 for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time but only 1 g of Pd/C was charged to the reaction mixture. The combined reaction mixture
20 was filtered and concentrated in vacuo to give 46.8 g of **45** as brown oil.

**Step 3. (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and
25 (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)**

To a solution of 27.3 g (73.4 mmole) of **45** in 300 ml of

anhydrous THF cooled to 2 °C with an ice bath was added 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred for 20 min, quenched with 300 ml of 10% HCl and extracted with methylene
5 chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give 24.7 g of yellow oil. Purification by HPLC (ethyl acetate-hexane) yielded 9.4 g of recovered **45** in the first fraction, 5.5 g (20%) of **6c** in the second
10 fraction and 6.5 g (24%) of **6d** in the third fraction.

B. Preparation from 2-hydroxydiphenylmethane**Step 1. 2-mercaptodiphenylmethane (46)****46**

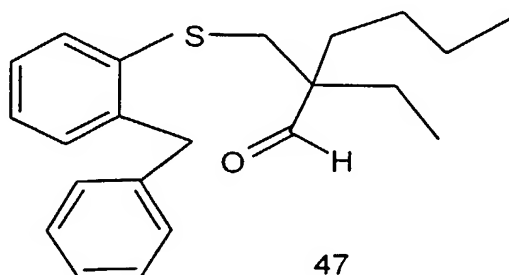
15 To a 500 ml flask was charged 16 g (0.33 mol) of 60% sodium hydride oil dispersion. The sodium hydride was washed twice with 50 ml of hexane. To the reaction flask was charged 100 ml of DMF. To this mixture was added a solution of 55.2 g (0.3 mol) of 2-
20 hydroxydiphenylmethane in 200 ml of DMF in 1 h while temperature was maintained below 30 °C by an ice-water bath. After complete addition of the reagent, the mixture was stirred at room temperature for 30 min then cooled with an ice bath. To the reaction mixture was
25 added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl chloride at once. The ice bath was removed and the reaction mixture was stirred at room temperature for 18 h before being poured into 300 ml of water. The organic was extracted into 500 ml of toluene. The toluene layer

SRL 6071
(C-3021/2)

269

was washed successively with 10% sodium hydroxide and brine and was concentrated in vacuo to give 78.6 g of a yellow oil which was 95% pure dimethyl O-2-benzylphenyl thiocarbamate. This oil was heated at 280-300 °C in a kugelrohr pot under house vacuum for 30 min. The residue was kugelrohr distilled at 1 torr (180-280 °C). The distillate (56.3 g) was crystallized from methanol to give 37.3 g (46%) of the rearranged product dimethyl S-2-benzylphenyl thiocarbamate as a yellow solid. A mixture of 57 g (0.21 mole) of this yellow solid, 30 g of potassium hydroxide and 150 ml of methanol was stirred overnight then was concentrated in vacuo. The residue was diluted with 200 ml of water and extracted with ether. The aqueous layer was made acidic with concentrate HCl, The oily suspension was extracted into ether. The ether extract was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of 2-mercaptodiphenylmethane as a yellow solid.

Step 2. 2-((2-Benzylphenylthio)methyl)-2-ethylhexanal (47)



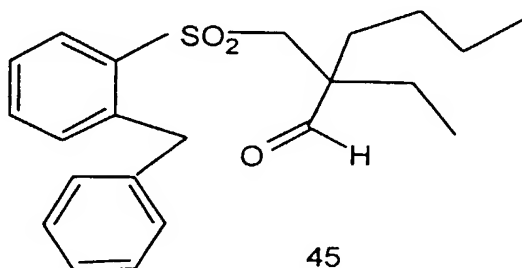
A mixture of 60 g (0.3 mole) of yellow solid from step 1, 70 g (0.3 mole) of compound 1 from preparation 1, 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-methoxyethyl ether was held at reflux for 6 hr and concentrated in vacuo. The residue was triturated with 500 ml of water and 30 ml of concentrate HCl. The

SRL 6071
(C-3021/2)

270

organic was extracted into 400 ml of ether. The ether layer was washed successively with brine, 10% sodium hydroxide and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2-5% ethyl acetate-hexane as eluent to give 2-((2-benzylphenylthio)methyl)-2-ethylhexanal **47** as a yellow syrup.

Step 3. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



To a solution of 72.8 g (0.21 mole) of yellow syrup from step 2 in 1 liter of methylene chloride cooled to 10 °C was added 132 g of 50-60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50-60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered through Celite. The methylene chloride solution was washed twice with 1 liter of 1 M potassium carbonate then with 1 liter of brine. The methylene chloride layer was dried over magnesium sulfate and concentrated to 76 g of 2-((2-benzylphenylsulfonyl)methyl)-2-ethylhexanal **45** as a syrup.

Step 4. (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)

SRL 6071
(C-3021/2)

271

Reaction of **45** with potassium t-butoxide according to the procedure in step 3 of procedure A gave pure **6c** and **6d** after HPLC.

5

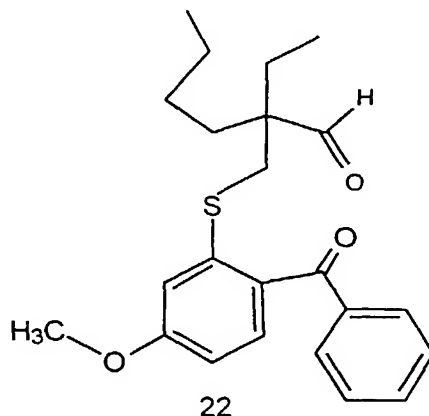
Example 19

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**25**)

10

and (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**26**)

Step 1. Preparation of 2-((2-benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (**22**)



15

2-Hydroxy-4-methoxybenzophenone was converted to the dimethyl O-2-benzoyphenyl thiocarbamate by methods previously described in example 18. The product can be isolated by recrystallization from ethanol. Using this improved isolation procedure no chromatography was needed. The thermal rearrangement was performed by reacting the thiocarbamate(5 g) in diphenyl ether at 260 °C as previously described. The improved isolation procedure which avoided a chromatography step was described below.

20

25

The crude pyrolysis product was then heated at 65 °C in

SRL 6071
(C-3021/2)

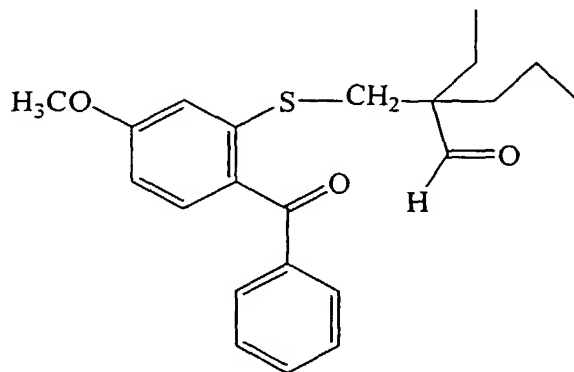
272

100 ml of methanol and 100 ml of THF in the presence of 3.5 g of KOH for 4 h. After removing THF and methanol by rotary evaporation the solution was extracted with 5 % NaOH and ether. The base layer was acidified and
5 extracted with ether to obtain a 2.9 g of crude thiophenol product. The product was further purified by titrating the desired mercaptan into base with limited KOH. After acidification and extraction with ether pure 2-mercapto-4-methoxybenzophenone (2.3 g) was isolated.

10

2-mercapto-4-methoxybenzophenone can readily be converted to the 2-((2-benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (22) by
15 reaction with 2-ethyl-2-(methoxymethyl)hexanal (1) as previously described.

Step 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (23)



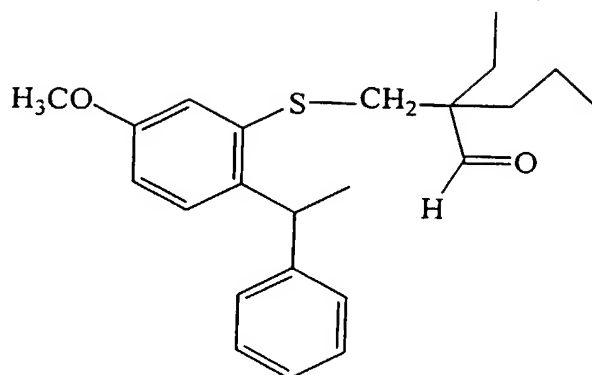
23

20 Substrate 22 was readily oxidized to 2-((2-benzoyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (23) as described in example 18.

Step 3. 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (24)
25

SRL 6071
(C-3021/2)

273



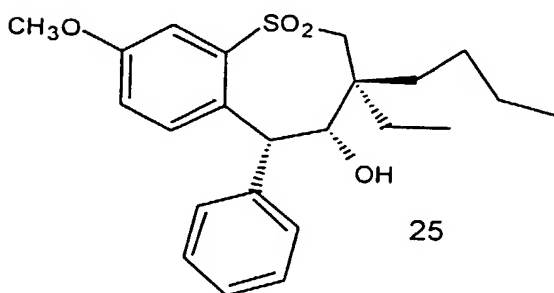
24

Sulfone **23** was then reduced to 2-((2-benzyl-5-methoxyphenyl-sulfonyl)methyl)-2-ethylhexanal (**24**) as described in example 18.

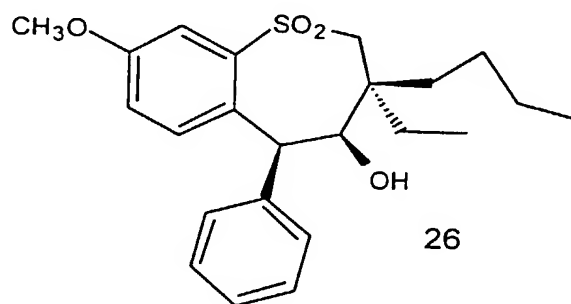
5

Step 4. (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**25**) and (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**26**)

10



25



26

A 3-neck flask equipped with a powder addition funnel, thermocouple and nitrogen bubbler was charged with 19.8 g (0.05 mole) of sulfone **24** in 100 ml dry THF. The reaction was cooled to -1.6 °C internal temperature by means of ice/salt bath. Slowly add 5.61 g (0.05 mole) of potassium t-butoxide by means of the powder addition funnel. The resulting light yellow

15

SRL 6071
(C-3021/2)

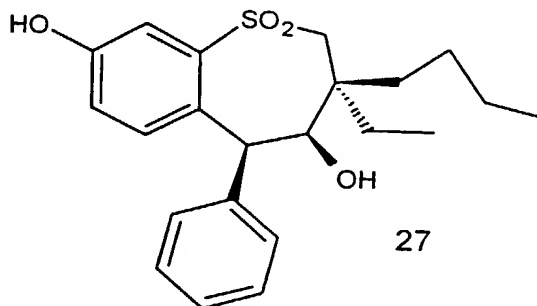
274

5 solution was maintained at -1.6 °C. After 30 min
reaction 400 ml of cold ether was added and this
solution was extracted with cold 10 % HCl. The acid
layer was extracted with 300 ml of methylene chloride.
10 The organic layers were combined and dried over
magnesium sulfate and after filtration stripped to
dryness to obtain 19.9 g of product. ¹H nmr and glpc
indicated a 96% conversion to a 50/50 mixture of **25** and
26. The only other observable compound was 4% starting
sulfone **24**.

15 The product was then dissolved in 250 ml of 90/10
hexane/ethyl acetate by warming to 50 °C. The solution
was allowed to cool to room temperature and in this way
pure **26** can be isolated. The crystallization can be
enhanced by addition of a seed crystal of **26**. After 2
crystallizations the mother liquor which was now 85.4%
20 **25** and has a dry weight of 8.7 g. This material was
dissolved in 100 ml of 90/10 hexane/ethyl acetate and
10 ml of pure ethyl acetate at 40 C. Pure **25** can be
isolated by seeding this solution with a seed crystal
of **25** after storing it overnight at 0 C.

Example 20

25 (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4,8-dihydroxy-5-phenyl-
2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**27**)



In a 25 ml round bottomed flask, 1 g of **26**(2.5 mmols)

SRL 6071
(C-3021/2)

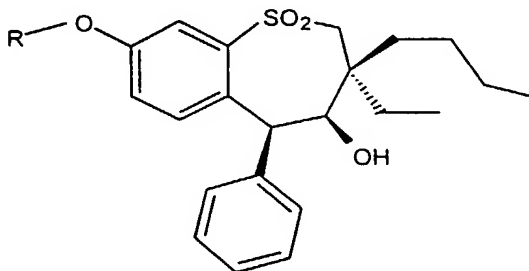
275

and 10 ml methylene chloride were cooled to - 78 °C with stirring. Next 0.7 ml of boron tribromide (7.5 mmole) was added via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 6 h. The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water. The organic layer was dried over magnesium sulfate. The product (0.88g) **27** was characterized by NMR and mass spectra.

Example 21

General Alkylation of phenol **27**

A 25 ml flask was charged with 0.15 g of **27** (0.38 mmole), 5 ml anhydrous DMF, 54 mg of potassium carbonate (0.38 mmole) and 140 mg ethyl iodide (0.9 mmole). The reaction was stirred at room temperature overnight. The reaction was diluted with 50 ml ethyl ether and washed with water (25 ml) then 5% NaOH (20 ml) and then sat. NaCl. After stripping off the solvent the ethoxylated product **28** was obtained in high yield. The product was characterized by NMR and mass spectra. This same procedure was used to prepare products listed in table 1 from the corresponding iodides or bromides. For higher boiling alkyl iodides and bromides only one equivalent of the alkyl halide was used.



Formula for Table 1

SRL 6071
(C-3021/2)

276

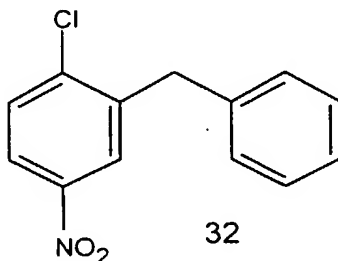
Table 1

| Compound No. | R |
|--------------|---|
| 27 | H |
| 26 | Me |
| 28 | Et |
| 29 | hexyl |
| 30 | Ac |
| 31 | (CH ₂) ₆ -N-pthalimide |

Example 22

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (37) and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (38)

Step 1. Preparation of 2-chloro-5-nitrodiphenylmethane (32)



Procedure adapted from reference :Synthesis -Stuttgart
9 770-772 (1986) Olah G. Et al

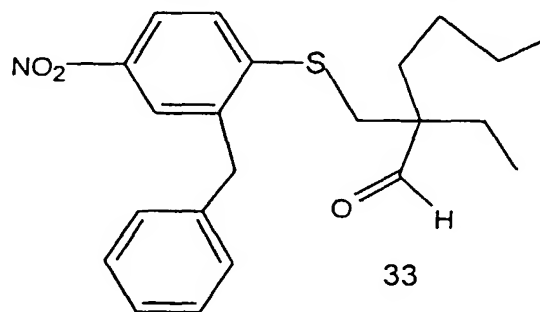
Under nitrogen, a 3 neck flask was charged with 45 g (0.172 mole) of 2-chloro-5-nitrobenzophenone in 345 ml methylene chloride and the solution was cooled to ice/water temperature. By means of an additional funnel, 150 g(0.172 mole) of trifluoromethane sulfonic acid in 345 ml methylene chloride was added slowly. Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride was added dropwise to the chilled

SRL 6071
(C-3021/2)

277

5 solution. Both addition steps(trifluoromethane
sulfonic acid and triethylsilane)were repeated. After
the additions were completed the reaction was allowed
to slowly warm up to room temperature and stirred for
12 h under nitrogen. The reaction mixture was then
10 poured into a chilled stirred solution of 1600 ml of
saturated sodium bicarbonate. Gas evolution occurred.
Poured into a 4 liter separatory funnel and separated
layers. The methylene chloride layer was isolated and
combined with two 500 ml methylene chloride extractions
15 of the aqueous layer. The methylene chloride solution
was dried over magnesium sulfate and concentrated in
vacuo. The residue was recrystallized from hexane to
give 39 g product. Structure 32 was confirmed by mass
spectra and proton and carbon NMR.

Step 2. Preparation of 2-((2-benzyl-4-nitrophenylthio)methyl)-2-ethylhexanal (33)



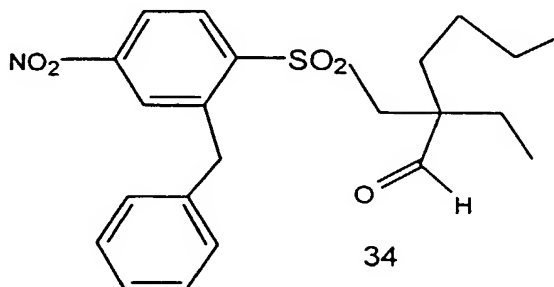
20 The 2-chloro-5-nitrodiphenylmethane product **32** (40 g,
0.156 mole) from above was placed in a 2 liter 2 neck
flask with water condenser. Next 150 ml DMSO and 7.18 g
(0.156 mole) of lithium sulfide was added and the
solution was stirred at 75 °C for 12 h. The reaction
25 was cooled to room temperature and then 51.7 g of
mesylate IV was added in 90 ml DMSO. The reaction
mixture was heated to 80 °C under nitrogen. After 12 h
monitored by TLC and added more mysylate if necessary.

SRL 6071
(C-3021/2)

278

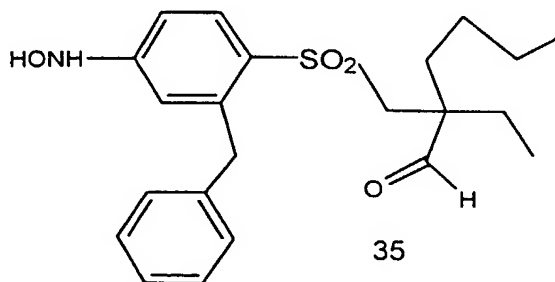
Continued the reaction until the reaction was completed. Next the reaction mixture was slowly poured into a 1900 ml of 5% acetic aqueous solution with stirring, extracted with 4 X 700 ml of ether, and dried over MgSO₄. After removal of ether, 82.7 g of product was isolated. The material can be further purified by silica gel chromatography using 95% hexane and 5 % ethyl acetate. If pure mysylate was used in this step there was no need for further purification. The product 33 was characterized by mass spectra and NMR.

Step 3. Oxidation of the nitro product 33 to the sulfone 2-((2-benzyl-4-nitrophenylsulfonyl)methyl)-2-ethylhexanal (34)



The procedure used to oxidize the sulfide 33 to the sulfone 34 has been previously described.

Step 4. Reduction of 34 to 2-((2-benzyl-4-hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (35)



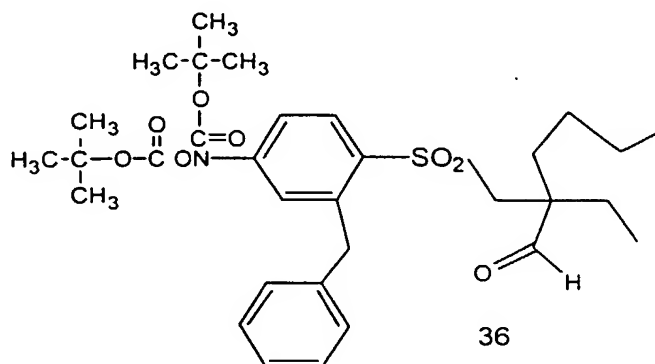
A 15 g sample of 34 was dissolved in 230 ml of ethanol

SRL 6071
(C-3021/2)

279

and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt.% Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate **34** was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product **35** was isolated by filtering off the Pd/C and then stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

Step 5. Preparation of the 2-((2-benzyl-4-N,O-di-(t-butoxy-carbonyl)hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (36).



A 13.35 g sample of **35** (0.0344 mole) in 40 ml of dry THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of di-t-butyl dicarbonate in 7 ml THF. Heated at 60 °C overnight. Stripped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.

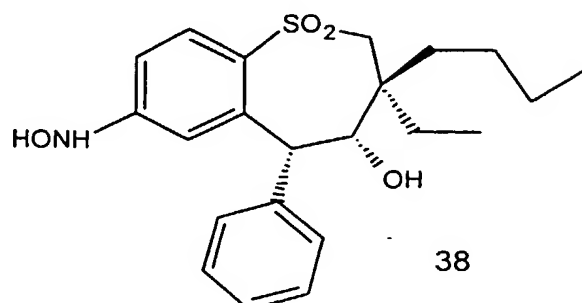
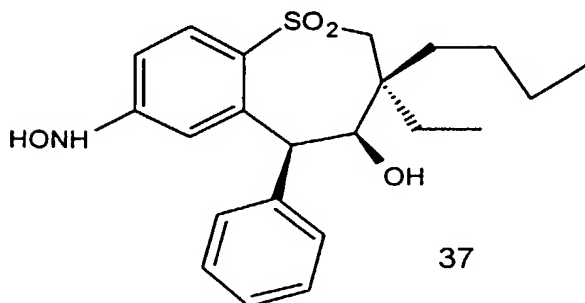
The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product **36** was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.

Step 6. (3α,4α,5α) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-

SRL 6071
(C-3021/2)

280

1,1-dioxide (37) and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (38)



- 5 A 250ml 3-neck round bottomed flask was charged with 4 g of **36** (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78 °C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide (20.4 mmoles) with stirring and maintaining a -78 °C reaction temperature.
- 10 After 1 h at -78 °C the addition of base was completed and the temperature was brought to -10 °C by means of a ice/salt bath. After 3 h at -10 °C, only trace **36** remained by TLC. Next add 35 ml of deionized water to the reaction mixture at -10 °C and stirred for 5 min.
- 15 Striped off most of the THF and added to separatory funnel and extracted with ether until all of the organic was removed from the water phase. The combined ether phases were washed with saturated NaCl and then dried over sodium sulfate. The only products by TLC and
- 20 NMR were the two BOC protected isomers of **37** and **38**. The isomers were separated by silica gel chromatography using 85% hexane and 15 % ethyl acetate; **BOC-37** (0.71 g) and **BOC- 38** (0.78 g).
- 25 Next the BOC protecting group was removed by reacting 0.87 g of **BOC-38** (1.78 mmoles) with 8.7 ml of 4 M HCl (34.8 mmoles) in dioxane for 30 min. Next added 4.74 g

SRL 6071
(C-3021/2)

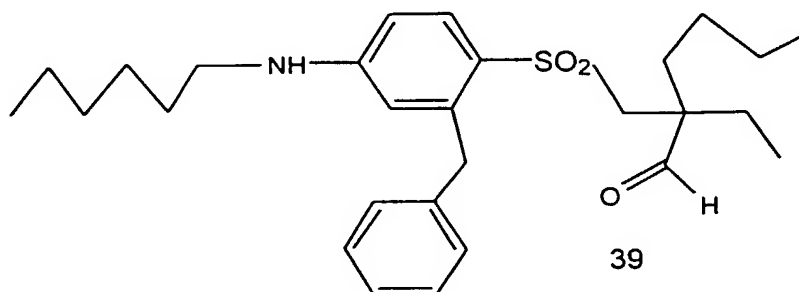
281

of sodium acetate (34.8 mmoles) to the reaction mixture and 16.5 ml ether and stirred until clear. After transferring to a separatory funnel extracted with ether and water and then dried the ether layer with sodium sulfate. After removing the ether, 0.665 g of **38** was isolated. Isomer **37** could be obtained in a similar procedure.

Example 23

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**40**) and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**41**)

Step 1. 2-((2-Benzyl-4-(n-hexylamino)phenylsulfonyl)methyl)-2-ethylhexanal (**39**)

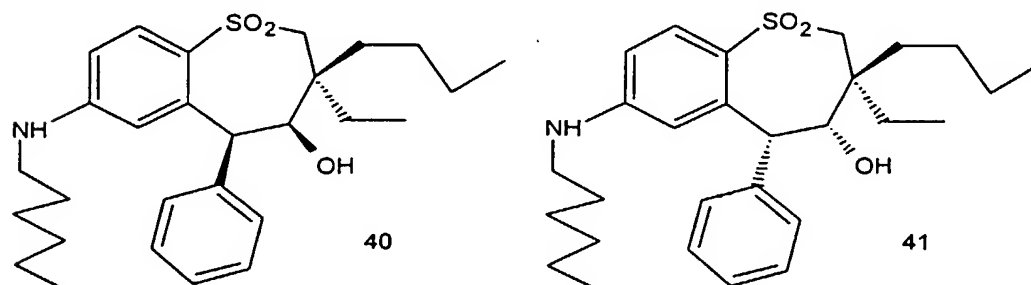


In a Fischer porter bottle weighed out 0.5 g of **34** (1.2 mmoles) and dissolved in 3.8 ml of ethanol under nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexanal. Seal and pressure to 50 psi of hydrogen gas. Stirred for 48 h. After filtering off the catalyst and removing the solvent by rotary evaporation **39** was isolated by column chromatography (0.16 g) using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. The product was characterized by NMR and mass spectra.

SRL 6071
(C-3021/2)

282

Step 2. (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**40**) and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**41**)



A 2-neck, 25 ml round bottomed flask with stir bar was charged with 0.158 g **39** (0.335 mmole) and 5 ml anhydrous THF under nitrogen. Cool to -10 °C by means of a salt/water bath. Slowly add 0.113 g of potassium tert butoxide (0.335 mmole). After 15 min at -10 °C all of the starting material was consumed by TLC and only the two isomers **40** and **41** were observed. Next added 5 ml of chilled 10% HCl and stirred at -10 °C for 5 min. Transferred to a separatory funnel and extract with ether. Dried over sodium sulfate. Proton NMR of the dried product (0.143 g) indicated only the presence of the two isomers **40** and **41**. The two isomers were separated by silica gel chromatography using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. **40** (53.2 mg); **41**(58.9 mg).

Example 24

Quaternization of amine substrates **40** and **41**

Amine products such as **40** and **41** can be readily

SRL 6071
(C-3021/2)

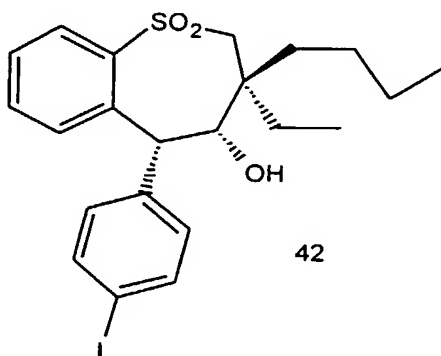
283

alkylated to quaternary salts by reaction with alkyl halides. For example **40** in DMF with 5 equivalents of methyl iodide in the presence of 2,6 dimethyl lutidine produces the dimethylhexylamino quaternary salt.

5

Example 25

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**42**)



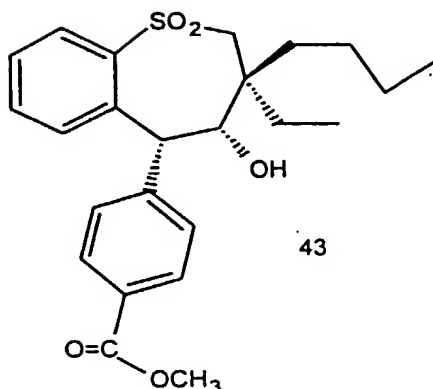
10 In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of **6d**
15 , 0.67 g of mercuric triflate were dissolved in 20 ml
of dry methylene chloride with stirring. Next 0.34 g of
Iodine was added and the solution was stirred at room
temperature for 30 h. The reaction was then diluted
with 50 ml methylene chloride and washed with 10 ml of
1 M sodium thiosulfate; 10 ml of saturated KI ; and
dried over sodium sulfate. See Tetrahedron, Vol.50,
No. 17, pp 5139-5146 (1994) Bachki, F. Et al. Mass
spectrum indicated a mixture of **6d** , mono iodide **42** and
a diiodide adduct. The mixture was separated by column
chromatography and **42** was characterized bt NMR and mass
spectra.

Example 26

25 (3 α ,4 β ,5 β) 3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4-
hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
(**43**)

SRL 6071
(C-3021/2)

284



A 0.1 g sample of **42** (0.212 mmole), 2.5 ml dry
methanol, 38 μ l triethylamine (0.275 mmole) , 0.3 ml
toluene and 37 mg of palladium chloride (0.21 mmole)
was charged to a glass lined mini reactor at 300 psi
carbon monoxide. The reaction was heated at 100 °C
overnight. The catalyst was filtered and a high yield
of product was isolated.
The product was characterized by NMR and mass spectra.

Note the ester functionalized product **43** can be
converted to the free acid by hydrolysis.

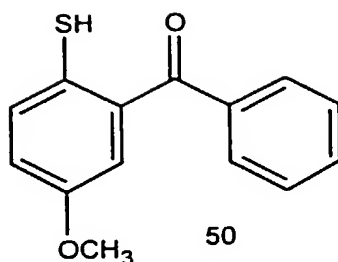
Example 27

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-
phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
(**48**), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-
methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-
dioxide (**49**)

Step 1. 2-Mercapto-5-methoxybenzophenone (**50**)

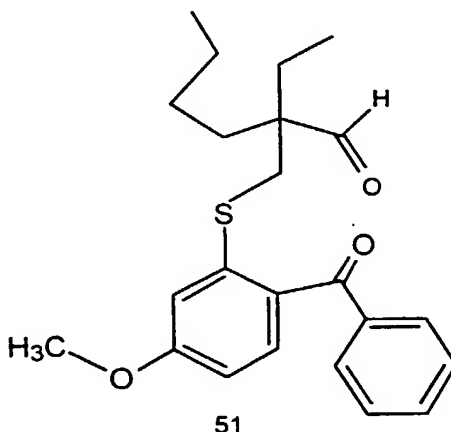
SRL 6071
(C-3021/2)

285



Reaction of 66.2 g of 4-methoxythiophenol with 360 ml of 2.5 N n-butyllithium, 105 g of tetramethylethylenediamine and 66.7 g of benzonitrile in 600 ml cyclohexane according to the procedure in WO 93/16055 gave 73.2 g of brown oil which was kugelrohr distilled to remove 4-methoxythiophenol and gave 43.86 g of crude 50 in the pot residue.

Step 2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (51)



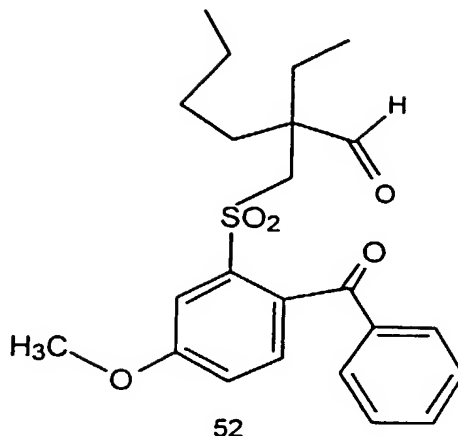
Reaction of 10 g (0.04 mole) of crude 50 with 4.8 g (0.02 mole) of mesylate 1 and 3.2 ml (0.23 mole) of triethylamine in 50 ml of diglyme according to the procedure for the preparation of 2 gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-hexane) to give 1.7 g (22%) of 51.

Step 3. 2-((2-Benzoyl-4-methoxyphenylsulfonyl)methyl)-

SRL 6071
(C-3021/2)

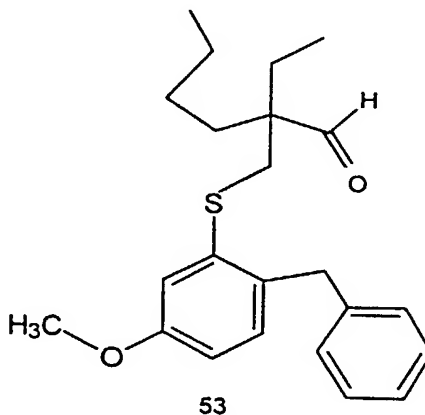
286

2-ethyl-hexanal (52)



A solution of 1.2 g (3.1 mmoles) of **51** in 25 ml of methylene chloride was reacted with 2.0 g (6.2 mmoles) of 50-60% MCPBA according to the procedure of step 2 of procedure A in example 18 gave 1.16 g (90%) of **52** as a yellow oil.

Step 4. 2-((2-Benzyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (53)



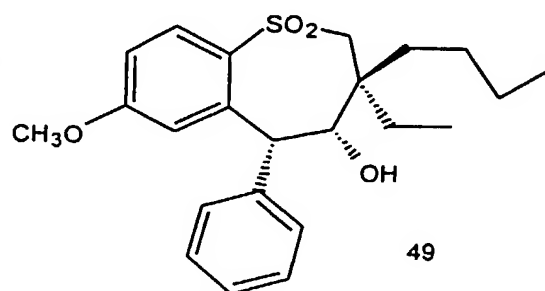
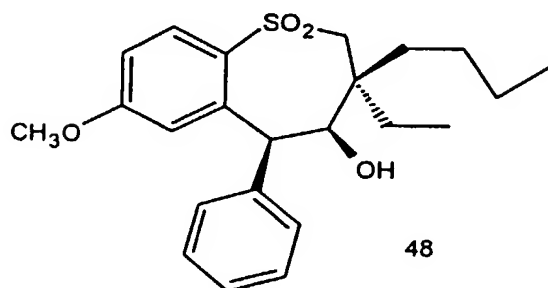
Hydrogenation of 1.1 g of **52** according to the procedure of step 3 of procedure A of example 18 gave **53** as a yellow oil (1.1 g).

Step 5. (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide

SRL 6071
(C-3021/2)

287

(48), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (49)

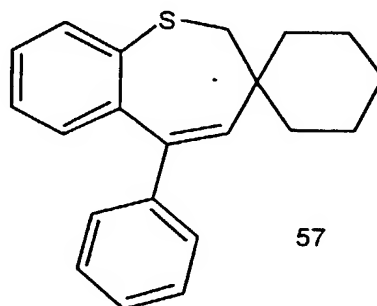
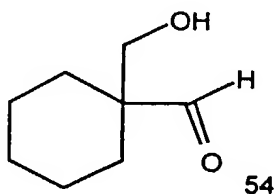


5 A solution of 1.1 g of 53, 0.36 g of potassium t-butoxide and 25 ml of anhydrous THF was held at reflux for 2 h and worked up as in step 4 of procedure A of example 18 to give 1.07 g of a crude product which was purified by HPLC to give 40 mg (4%) of 48 as crystals, mp 153-154 °C and 90 mg (8%) of 49 as solid, mp 136-140 °C.

Example 28

15 5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)

Step 1. 1-(Hydroxymethyl)-cyclohexanecarboxaldehyde (54)



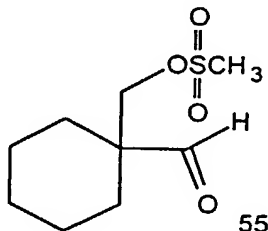
20 To a cold (0 °C) mixture of 100 g (0.891 mole) of cyclohexanecarboxaldehyde, 76.5 g of 37% of formaldehyde in 225 ml of methanol was added dropwise

SRL 6071
(C-3021/2)

288

90 ml of 1 N Sodium hydroxide in 1 h. The reaction mixture was stirred at room temperature over 48 then was evaporated to remove methanol. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 75 g (59.7%) of thick oil. Proton NMR and mass spectra were consistent with the product.

Step 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde (55)

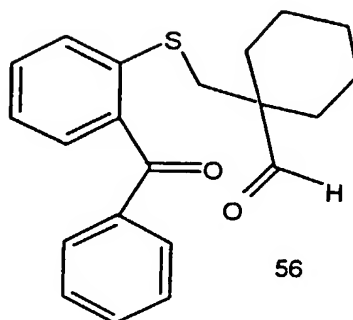


To a cold (0 °C) mixture of alcohol **54** (75 g, 0.54 mole) and 65.29 g (0.57 mole) of methanesulfonyl chloride in 80 ml of methylene chloride was added a solution of pyridine (47.96 g, 0.57 mole) in 40 ml of methylene chloride. The reaction mixture was stirred at room temperature for 18 h then quenched with water, acidified with conc. HCl and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 91.63 g (77.8%) of thick oil. Proton NMR and mass spectra were consistent with the product.

Step 3. 1-((2-Benzoylphenylthio)methyl)cyclohexanecarboxaldehyde (56)

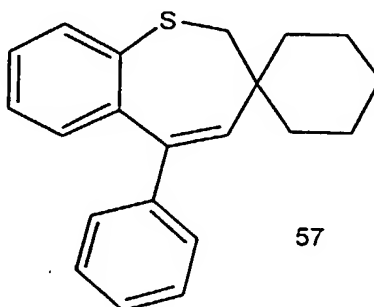
SRL 6071
(C-3021/2)

289



5 A mixture of 69 g (0.303 mole) of 2-mercaptobenzophenone, 82 g (0.303 mole) of mesylate **55**, 32 g of triethylamine, and 150 ml of diglyme was stirred and held at reflux for 24 h. The mixture was cooled, poured into dil. HCl and extracted with methylene chloride. The organic layer was washed with 10% NaOH, water, brine, and dried over sodium sulfate and concentrated under vacuum to remove excess diglyme. 10 This was purified by silica gel flush column (5% EtOAc: Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton NMR and mass spectra were consistent with the product.

15 **Step 4. 5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)**



20 To a mixture of 6.19 g of zinc dust and 100 ml of dry DME was added TiCl_3 (16.8 g, 0.108 mole). The reaction mixture was heated to reflux for 2 h. A solution of compound **56** (8.3 g, 0.023 mole) in 50 ml of DME was added dropwise to the reaction mixture in 1 h and the

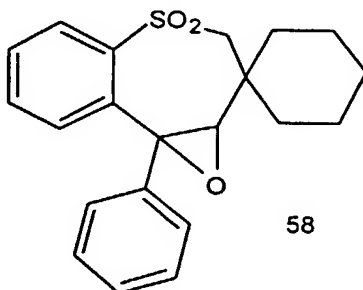
SRL 6071
(C-3021/2)

290

mixture was held at reflux for 18 h. The mixture was cooled, poured into water and extracted with ether. The organic layer was washed with water, brine, and dried over sodium sulfate, filtered through celite and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white solid, mp 90-91 °C. Proton and carbon NMR and mass spectra were consistent with the product.

Example 29

8b-Phenyl-1a,2,3,8b-tetrahydrospiro(benzothiepine[4,5-b]oxirene-2,1'-cyclohexane)-4,4-dioxide (58)



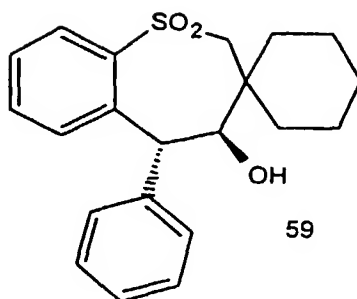
To a solution of 57 (4.6 g, 15 mmole) in 50 ml chloroform under nitrogen was added 55% MCPBA (16.5 g, 52.6 mmole) portionwise with spatula. The reaction was held at reflux for 18 h and washed with 10% NaOH(3X), water, brine, and dried over sodium sulfate and concentrated under vacuum to give 5 g of crude product. This was recrystallized from Hexane/EtOAc to give 4.31 g (81%) of yellow solid, mp 154-155 °C. Proton and carbon NMR and mass spectra were consistent with the product.

Example 30

trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (59)

SRL 6071
(C-3021/2)

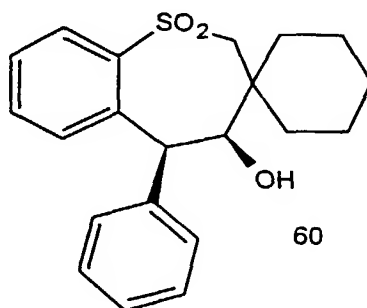
291



A mixture of 0.5 g (1.4 mmoles) of **58**, 20 ml of ethanol, 10 ml of methylene chloride and 0.4 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to dryness. The residue was purified by HPLC (10% EtOAc-Hexane, 25% EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was a trans isomer. The second fraction gave 200 mg of solid which was impure cis isomer.

Example 31

cis-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydrospiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (60)



To a solution of 0.2 g (0.56 mmole) of **59** in 20 ml of CH₂Cl₂, was added 8 g of 50% NaOH and one drop of Aliquat-336 (methyltricaprylammonium chloride) phase transfer catalyst. The reaction mixture was stirred for 10 h at room temperature. Twenty g of ice was added to the mixture and the mixture was extracted with CH₂Cl₂.

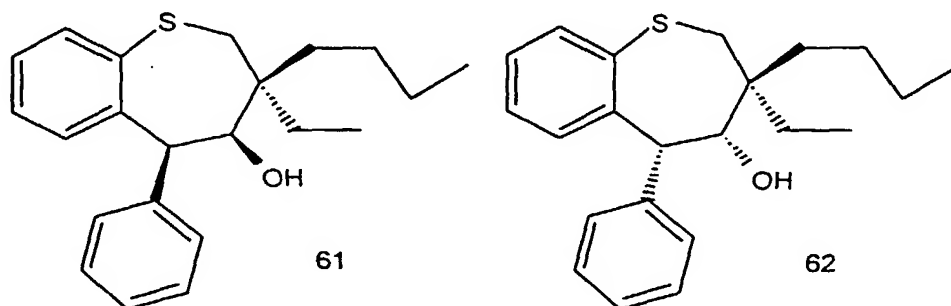
SRL 6071
(C-3021/2)

292

(3x10 ml) washed with water, brine and dried over MgSO_4 and concentrated in vacuo to recover 0.15 g of crude product. This was recrystallized from Hexane/EtOAc to give 125 mg of white crystal, mp 209-210 °C . Proton and carbon NMR and mass spectra were consistent with the product.

Example 32

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (61), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (62)



To a solution of 0.5 g (1.47 mmole) of compound 47 in 5 ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred at room temperature for 18 h and quenched with 10 ml of 10% HCl. The organic was extracted into methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by HPLC (2% EtOAc-hexane) to give 47 mg of 61 in the second fraction and 38 mg of 62 in the third fraction. Proton NMR and mass spectra were consistent with the assigned structures.

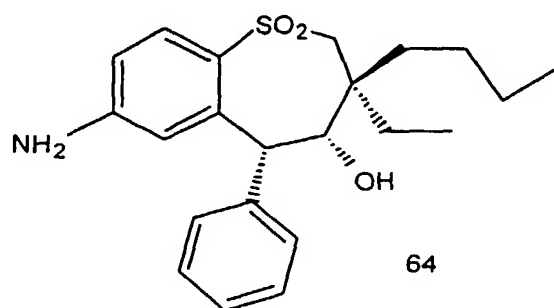
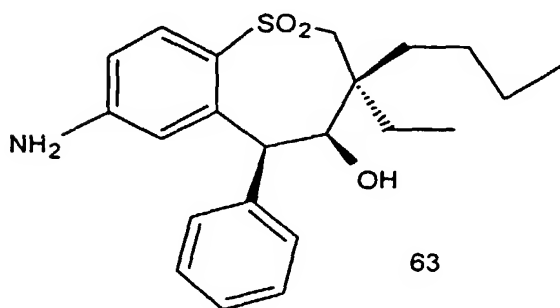
Example 33

(3 α ,4 α ,5 α) 3-Butyl-3ethyl-4-hydroxy-7-amino-5-phenyl-

SRL 6071
(C-3021/2)

293

2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (63) and
(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl-
2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (64)



5

An autoclave was charged with 200 mg of 37 in 40 cc ethanol and .02 g 10 % Pd/C. After purging with nitrogen the clave was charged with 100 psi hydrogen and heated to 55 C. The reaction was monitored by TLC and mass spec and allowed to proceed until all of 37 was consumed. After the reaction was complete the catalyst was filtered and the solvent was removed in vacuo and the only observable product was amine 63. This same procedure was used to produce 64 from 38.

15

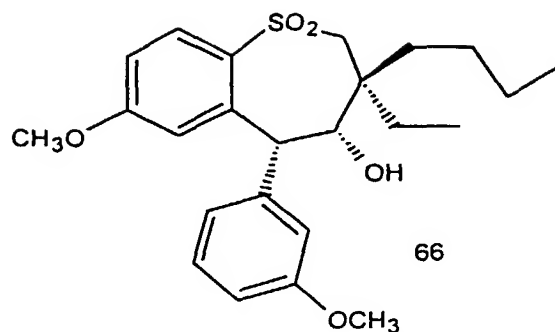
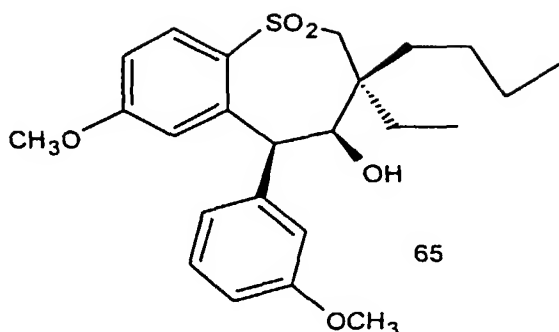
Example 34

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (65), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (66).

20

SRL 6071
(C-3021/2)

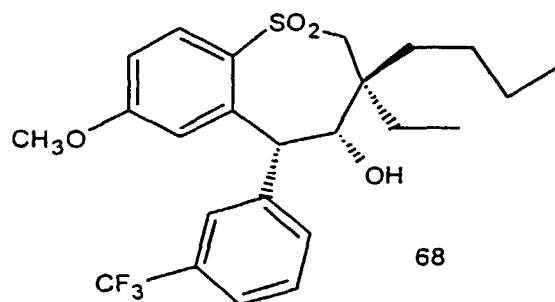
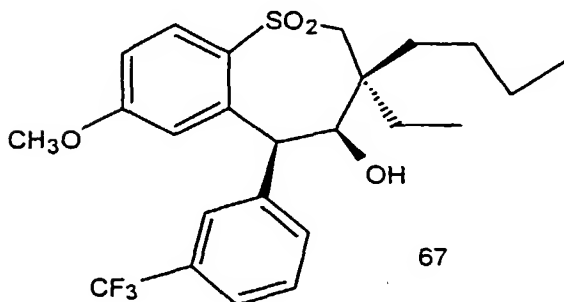
294



Alkylation of e-methoxyphenol with 3-methoxybenzyl
chloride according to the procedure described in J.
Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-
methoxybenzyl)phenol in 35% yield. This material was
converted to compound 65, mp 138.5-141.5 °C, and
compound 66, mp 115.5-117.5 °C, by the procedure
similar to that in Example 18 method B.

Example 35

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-
(trifluoromethyl)phenyl)-2,3,4,5-
tetrahydrobenzothiepine-1,1-dioxide (67), and
(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-
(trifluoromethyl)phenyl)-2,3,4,5-
tetrahydrobenzothiepine-1,1-dioxide (68).



Alkylation of 4-methoxyphenol with 3-
(trifluoromethyl)benzyl chloride according to the

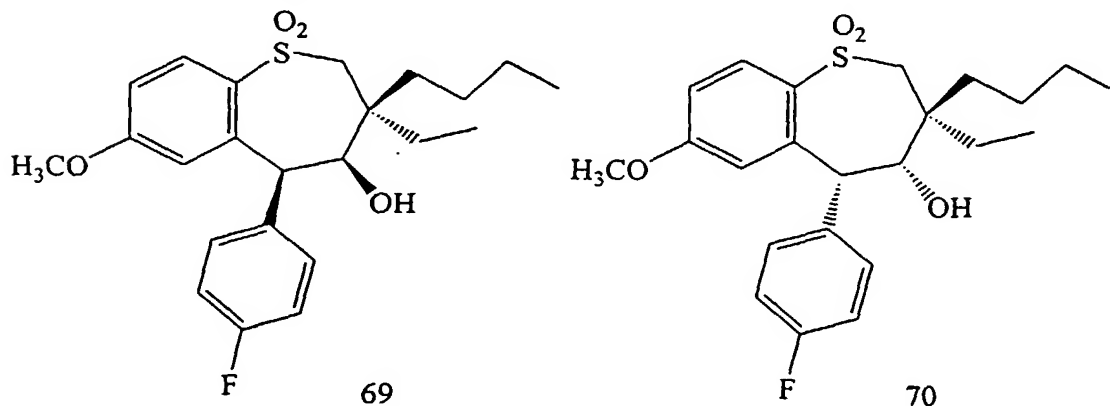
SRL 6071
(C-3021/2)

295

procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-(trifluoromethyl)benzyl)phenol. This material was converted to compound 67, mp 226.5-228 °C, and compound 68, mp 188-190°C, by the procedure similar to that in Example 18 method B.

Example 36

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (69), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (70).



Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(4'-fluorobenzyl)phenol. This material was converted to compound 69 and compound 70 by the procedure similar to that in Example 18 method B.

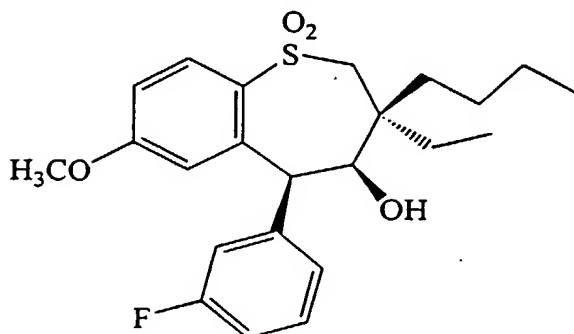
Example 37

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (71), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-

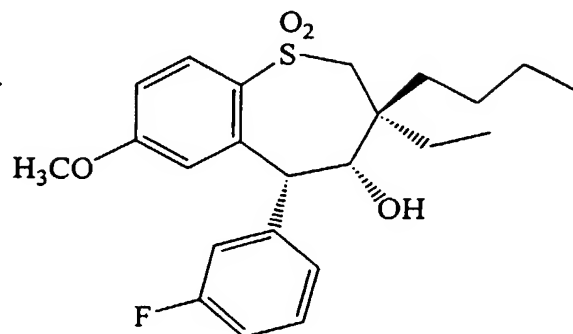
SRL 6071
(C-3021/2)

296

tetrahydrobenzothiepine-1,1-dioxide (72).



71

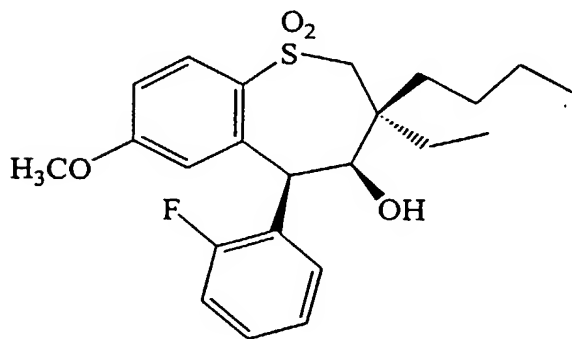


72

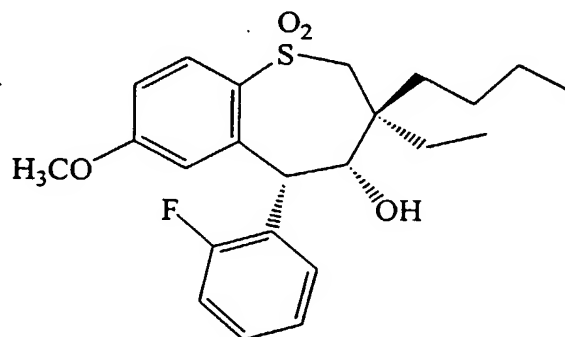
Alkylation of 4-methoxyphenol with 3-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-fluorobenzyl)phenol. This material was converted to compound 71 and compound 72 by the procedure similar to that in Example 18 method B.

Example 38

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).



73



74

Alkylation of 4-methoxyphenol with 2-fluorobenzyl

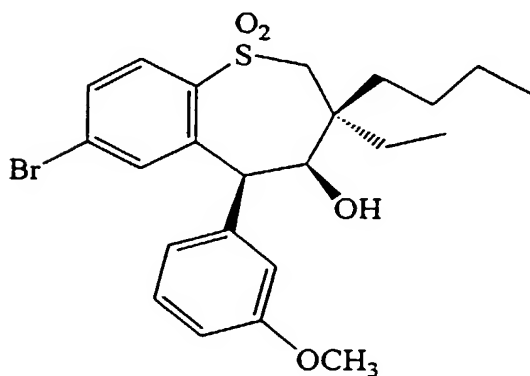
SRL 6071
(C-3021/2)

297

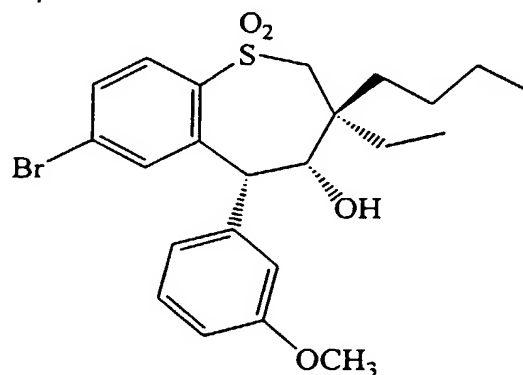
chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

Example 39

(3 α ,4 α ,5 α) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (75), and (3 α ,4 β ,5 β) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).



75



76

Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.

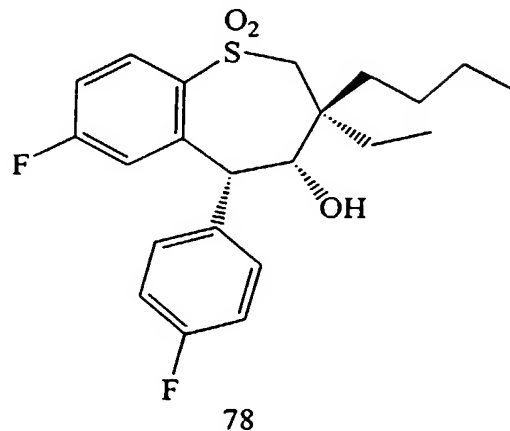
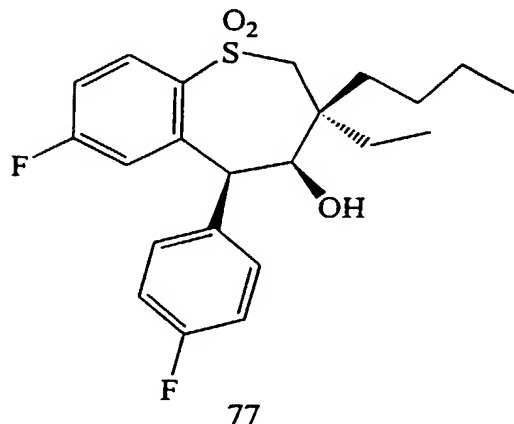
Example 40

(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (77), and

SRL 6071
(C-3021/2)

298

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (78).



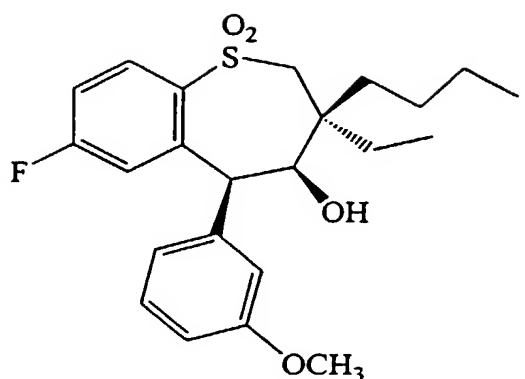
5 Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230 °C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

Example 41

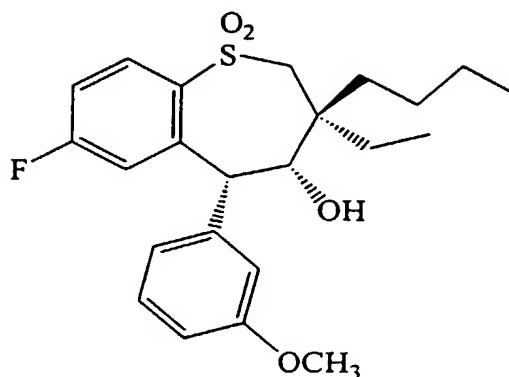
15 (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (80).

SRL 6071
(C-3021/2)

299



79

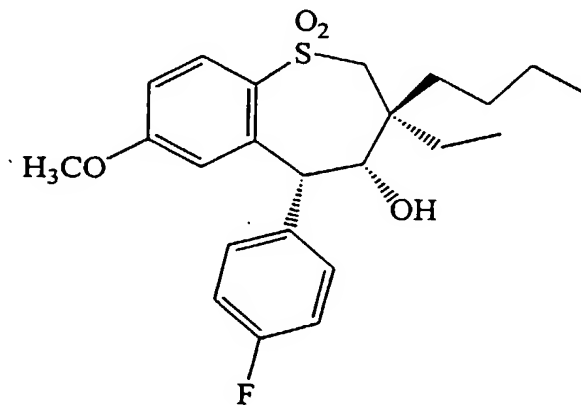


80

Alkylation of 4-fluorophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-methoxybenzyl)phenol. This material was converted to compound 79, as a solid and compound 80, mp 153-155 °C, by the procedure similar to that in Example 18 method B.

Example 42

(3 α , 4 β , 5 β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (81).



81

A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5

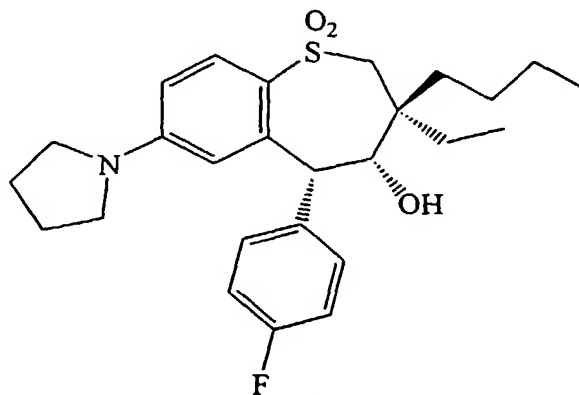
SRL 6071
(C-3021/2)

300

mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was dilute with ether and washed with water and brine and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20% ethyl acetate in hexanes). The first fraction was impure (3 α ,4 α ,5 α) 3-butyl-3-ethyl-4-hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide. The second fraction was compound 81, mp 185-186.5 °C.

Example 43

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-pyrrolidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (82).



82

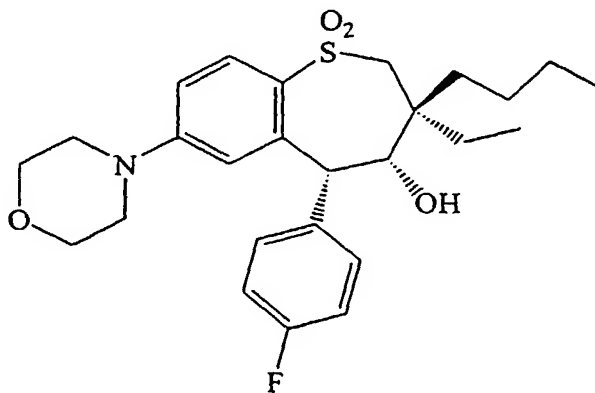
A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml of pyrrolidine was held at reflux for 1 h. The reaction mixture was diluted with ether and washed with water and brine and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was crystallized from ether-hexanes to give compound 82, mp 174.5-177 °C.

SRL 6071
(C-3021/2)

301

Example 44

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-morpholinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (83).



83

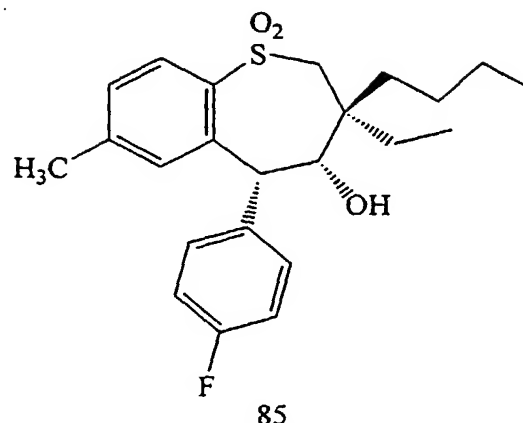
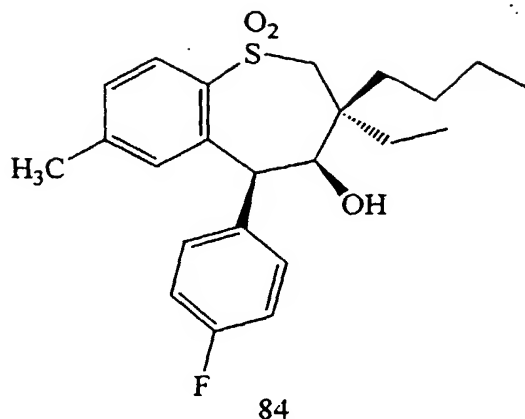
5 A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g
(56 mmol) of morpholine was held at reflux for 2 h and
concentrated in vacuo. The residue was diluted with
ether (30 ml) and washed with water and brine and dried
10 over M_gSO_4 . The ether solution was concentrated in
vacuo. The residue was recrystallized from ether-
hexanes to give compound 83, mp 176.5-187.5 °C.

Example 45

15 (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-
hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-
dioxide (84), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(4'-
fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-
tetrahydrobenzothiepine-1,1-dioxide (85).

SRL 6071
(C-3021/2)

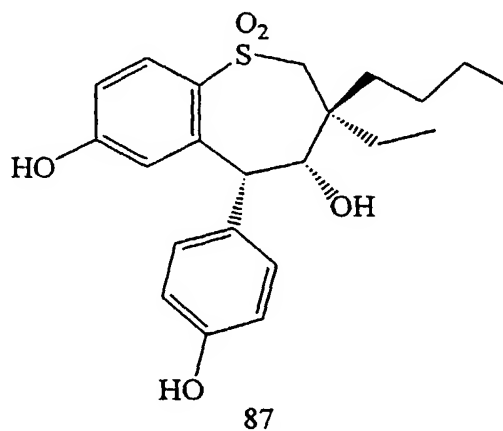
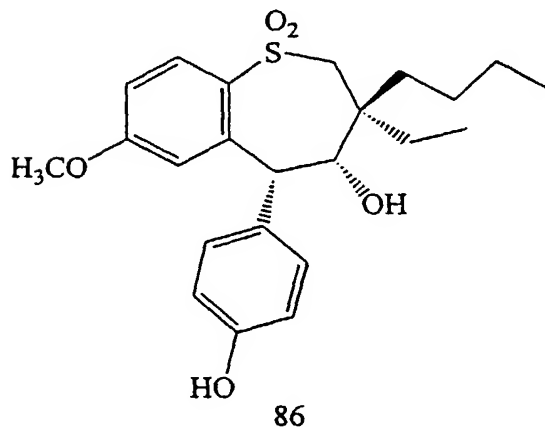
302



Alkylation of 4-methylphenol with 4-fluorobenzyl
chloride according to the procedure described in J.
Chem. Soc, 2431 (1958) gave 4-methyl-2-(4'-
5 fluorobenzyl)phenol). This material was converted to
compound 84 and compound 85 by the procedure similar to
that in Example 18 method B.

Example 46

10 (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-(4'-
hydroxyphenyl)-7-methoxy-2,3,4,5-
tetrahydrobenzothiepine-1,1-dioxide (86), and
(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-
15 hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-
dioxide (87).



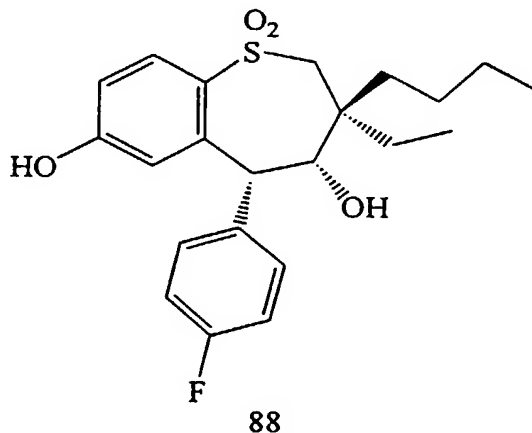
SRL 6071
(C-3021/2)

303

To a solution of 0.52 (1.2 mmol) of compound 66 in 20 ml of methylene chloride was added 1.7 g (6.78 mmol) of boron tribromide. The reaction mixture was cooled to -78 °C and was stirred for 4 min. An additional 0.3 ml of boron tribromide was added to the reaction mixture and the reaction mixture was stirred at -78 °C for 1 h and quenched with 2 N HCl. The organic was extracted into ether. The ether layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue (0.48 g) was purified by HPLC (30% ethyl acetate in hexanes). The first fraction was 0.11 g of compound 86 as a white solid, mp 171.5-173 °C. The second fraction was crystallized from chloroform to give 0.04 g of compound 87 as a white solid, mp 264 °C (dec).

Example 47

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (88).



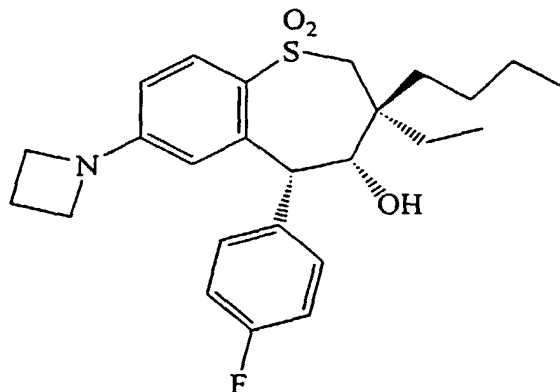
Reaction of compound 70 with excess boron tribromide at room temperature and worked up as in Example 46 gave compound 88 after an HPLC purification.

SRL 6071
(C-3021/2)

304

Example 48

(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-azetidiny)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (89).



89

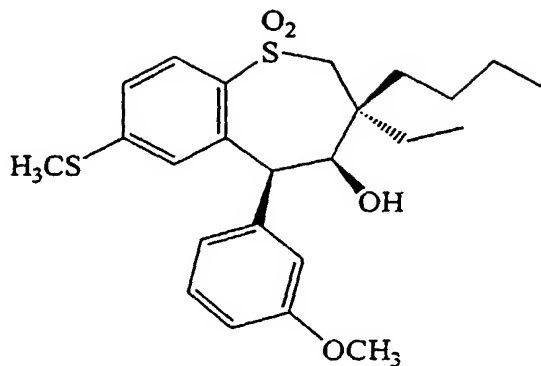
A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 g (35 mmol) of aztidine was held at reflux for 3 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over MgSO₄. The ether solution was concentrated on a steam bath. The separated crystals were filtered to give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.

Example 49

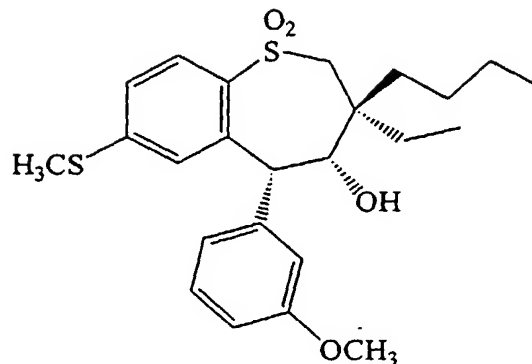
(3 α ,4 α ,5 α) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (90). (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (91).

SRL 6071
(C-3021/2)

305



90



91

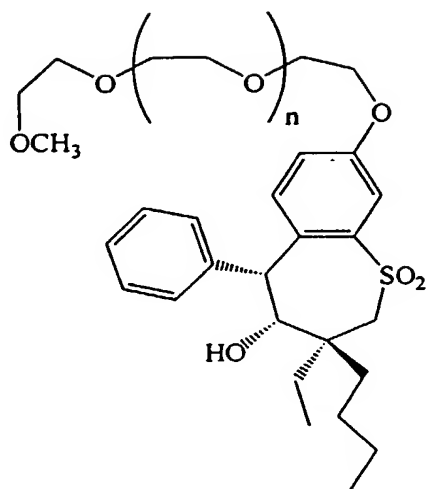
A mixture of 0.4 g (0.95 mmol) of compound 79, 0.08 g (1.14 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at 60 °C for 2 h. An additional 1.4 mmol of sodium methanethiolate was added to the reaction mixture and the mixture was stirred at 60 °C for an additional 2 h. The reaction mixture was triturated with 100 ml of water and extracted methylene chloride. The methylene chloride water mixture was filtered through Celite and the methylene chloride layer was dried over $MgSO_4$ and concentrated in vacuo. The first fraction (0.1 g) was compound 90, mp 117-121 °C. The second fraction (0.16 g) was compound 91, mp 68-76 °C.

Example 50

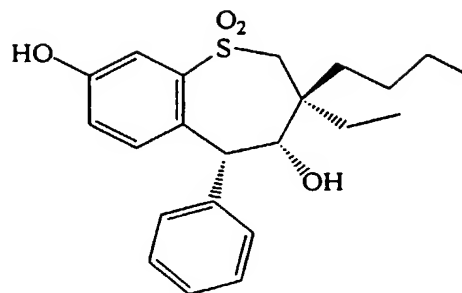
Preparation of polyethyleneglycol functionalized benzothiepine A.

SRL 6071
(C-3021/2)

306



No. 141



No. 136

A 50 ml rb flash under a nitrogen atmosphere was charged with 0.54 g of M-Tres-5000 (Polyethyleneglycol Tresylate [methoxy-PEG-Tres, MW 5000] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.055 g Compound No. 136, 0.326 C₃CO₃, and 2cc anhydrous acetonitrile. The reaction was stirred at 30 C for 5 days and then the solution was filtered to remove salts. Next, the acetonitrile was removed under vacuum and the product was dissolved in THF and then precipitated by addition of hexane. The polymer precipitate was isolate by filtration from the solvent mixture (THF/hexane). This precipitation procedure was continued until no Compound No. 136 was detected in the precipitated product (by TLC SiO₂). Next, the polymer precipitate was dissolved in water and filtered and the water soluble polymer was dialyzed for 48 hours through a cellulose dialysis tube (Spectrum® 7 ,45 mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried. The NMR was consistent with the desired product A and gel permeation chromatography indicated the presence of a 4500 MW polymer and also verified that no free Compound

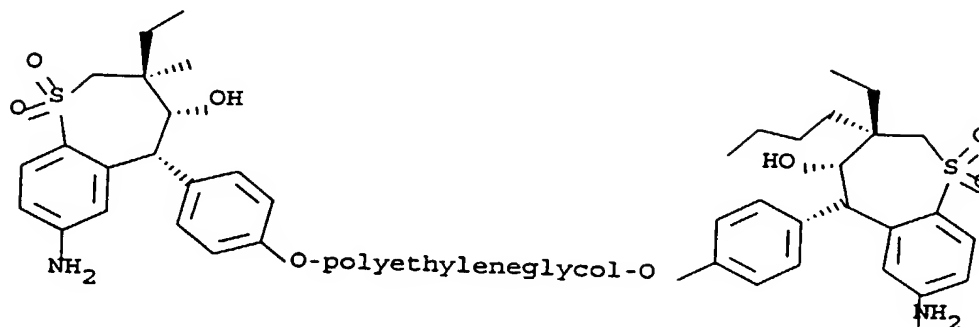
SRL 6071
(C-3021/2)

307

No. 136 was present. This material was active in the IBAT in vitro cell assay.

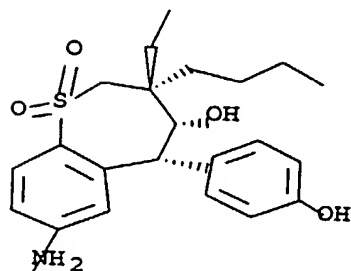
Example 51

5 Preparation of Compound 140



No. 140

10



No. 111

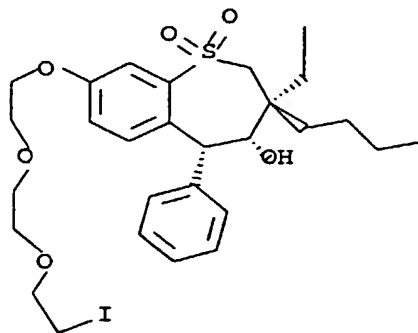
15 A 2-necked 50 ml round bottom Flask was charged with
0.42g of Tres-3400 (Polyethyleneglycol Tresylate [Tres-
PEG-Tres, MW 3400] purchased from Shearwater Polymers
Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama
35801), 0.1 potassium carbonate, 0.100g of Compound No.
20 111 and 5 ml anhydrous DMF. Stir for 6 days at 27 °C.
TLC indicated the disappearance of the starting
Compound No. 111. The solution was transferred to a

SRL 6071
(C-3021/2)

308

separatory funnel and diluted with 50 cc methylene chloride and then extracted with water. The organic layer was evaporated to dryness by means of a rotary evaporator. Dry wgt. 0.4875 g. Next, the polymer was dissolved in water and then dialyzed for 48 hours at 40 °C through a cellulose dialysis tube (spectrum® 7, 45mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried 0.341 g). NMR was consistent with the desired product B.

Example 52



No. 134

15

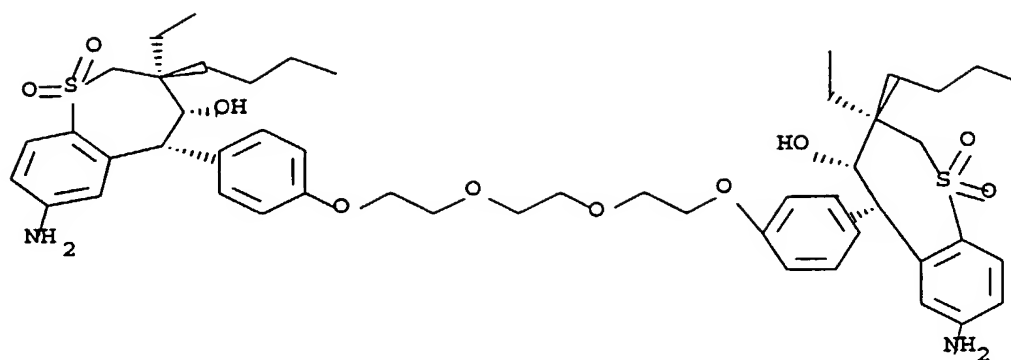
A 10 cc vial was charged with 0.21 g of Compound No. 136 (0.5mmoles), 0.17g (1.3 mmoles)potassium carbonate, 0.6g (1.5 mmoles) of 1,2-bis-(2-iodoethoxy)-ethane and 10 cc DMF. The reaction was stirred for 4 days at room temperature and then worked up by washing with ether/water. The ether layer was stripped to dryness and the desired product Compound No. 134 was isolated on a silica gel column using 80/20 hexane ethyl acetate.

25

Example 53

SRL 6071
(C-3021/2)

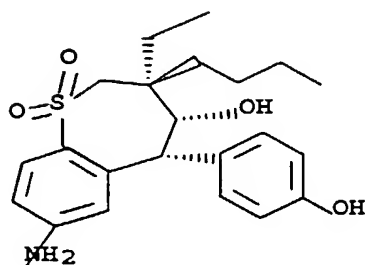
309



No. 112

5

Example 54



No. 113

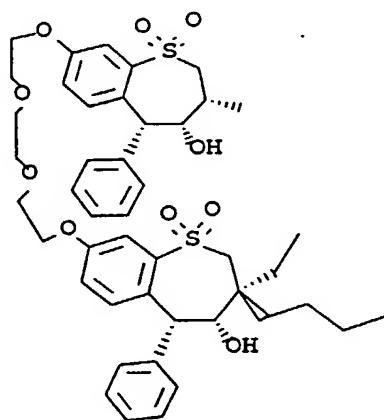
10

SRL 6071
(C-3021/2)

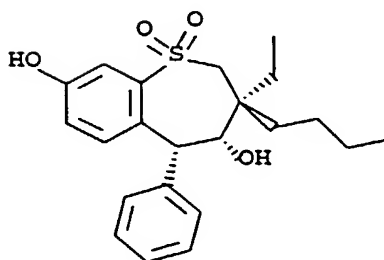
310

A two necked 25 ml round bottom Flask was charged with 0.5g (1.24mmoles) of 69462, 13 mls of anhydrous DMF, 0.055g of 60% NaH dispersion and 0.230g (0.62 mmoles) of 1,2-Bis [2-iodoethoxyethane] at 10 °C under nitrogen. Next, the reaction was slowly heated to 40 °C. After 14 hours all of the Compound No. 113 was consumed and the reaction was cooled to room temperature and extracted with ether/water. The ether layer was evaporated to dryness and then chromatographed on Silicage (80/20 ethyl acetate/hexane). Isolated Compound No. 112 (0.28 g) was characterized by NMR and mass spec.

Example 55



No. 135



No. 136

SRL 6071
(C-3021/2)

311

In a 50 ml round bottom Flask, add 0.7g (1.8 mmoles) of Compound No. 136, 0.621g of potassium carbonate, 6 ml DMF, and 0.33g of 1,2-Bis [2-iodoethoxyethane]. Stir at 40 °C under nitrogen for 12 hours. The workup and isolation was the same procedure for Compound No. 112.

Examples 56 and 57 (Compound Nos. 131 and 137)

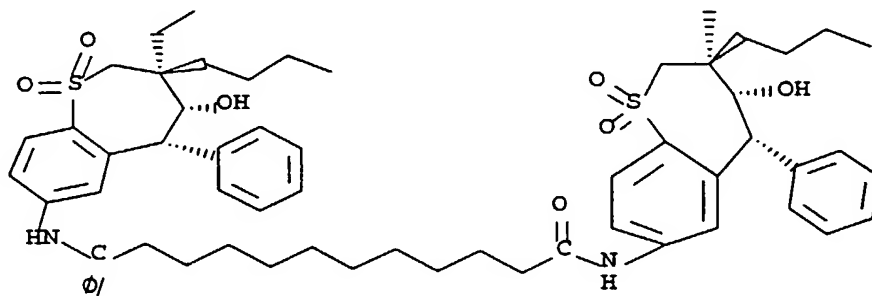
The compositions of these compounds are shown in Table 3.

The same procedure as for Example 55 except appropriate benzothiepine was used.

Example 58 (Compound No. 139)

The composition of this compound is shown in Table 3. Same procedure as for Example 55 with appropriate benzothiepine 1,6 diiodohexane was used instead of 1,2-Bis [2-iodoethoxyethane].

Example 59 (Compound No. 101)



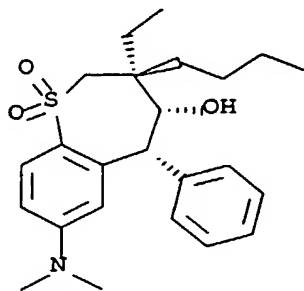
101

This compound is prepared by condensing the 7-NH₂ benzothiepine with the 1,12-dodecane dicarboxylic acid or acid halide.

SRL 6071
(C-3021/2)

312

Example 60 (Compound No. 104)



No. 104

5

2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII.

10

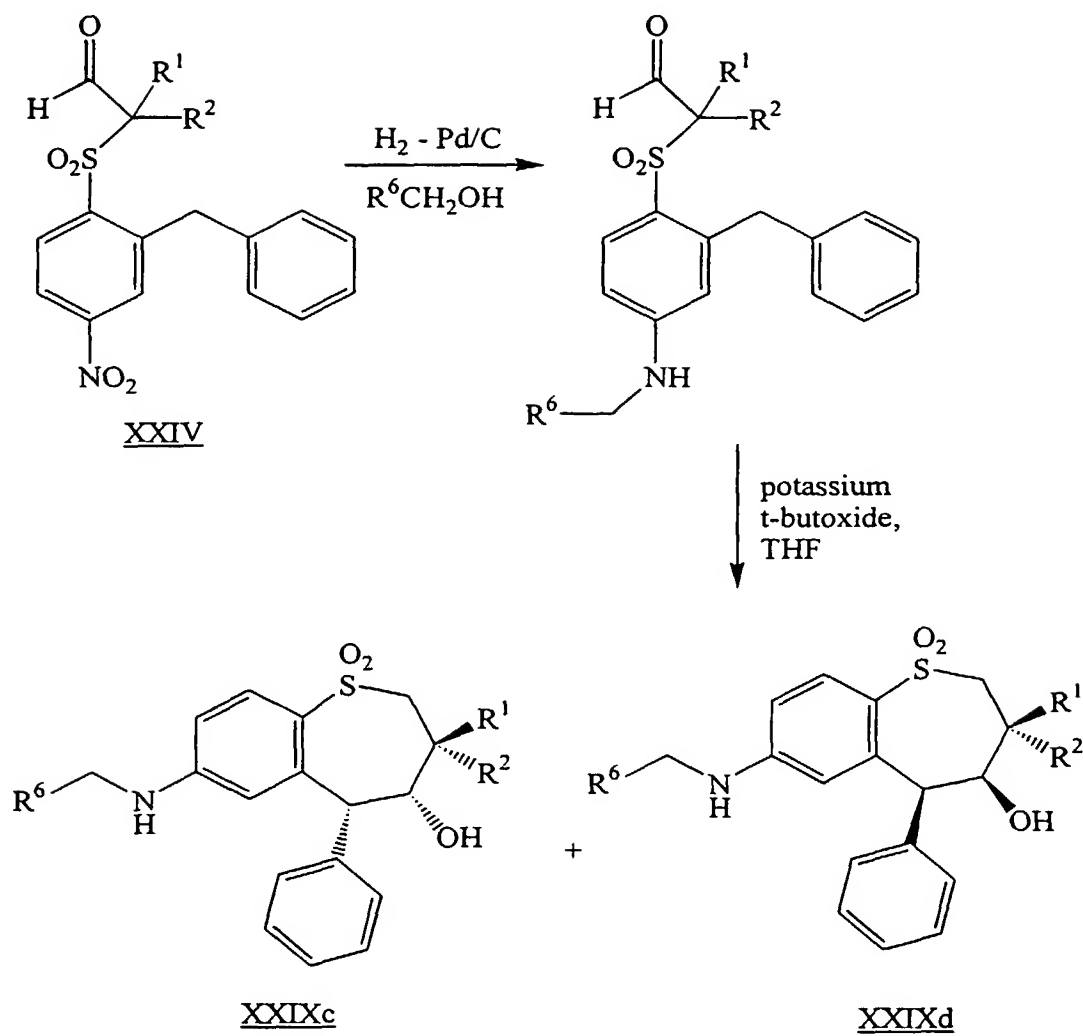
Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 5). Reduction of the sulfone-aldehyde XXV formaldehyde and 100 psi hydrogen and 55 C for 12 hours catalyzed by palladium on carbon in the same reaction vessel yields the substituted dimethylamine derivative XXVIII. Cyclization of XXVII with potassium t-butoxide yields a mixture of substituted amino derivatives of this invention Compound No. 104.

15

SRL 6071
(C-3021/2)

313

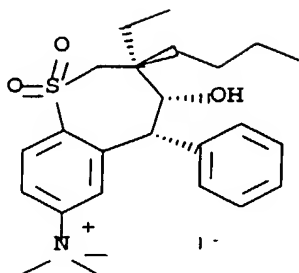
Scheme 6



SRL 6071
(C-3021/2)

314

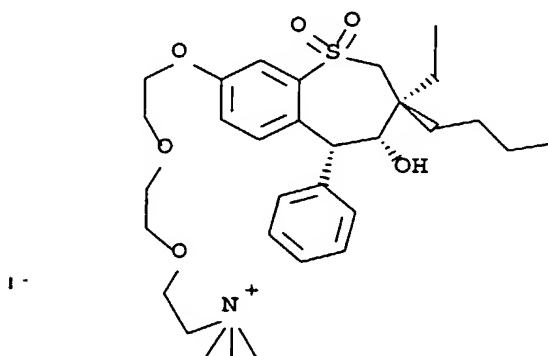
Example 61



No. 102

5 A 1 oz. Fisher-porter bottle was charged with 0.14 g
(0.34 mmoles) of 70112, 0.97 gms (6.8 mmoles) of methyl
iodide, and 7 ml of anhydrous acetonitrile. Heat to 50
°C for 4 days. The quat. Salt Compound No. 192 was
10 isolated by concentrating to 1 cc acetonitrile and then
precipitating with diethyl ether.

Example 62



No. 125

15 A 0.1 g (0.159 mmoles) sample of Compound No. 134 was
dissolved in 15 ml of anhydrous acetonitrile in a
Fischer-porter bottle and then trimethylamine was
bubbled through the solution for 5 minutes at 0 °C and
20 then capped and warmed to room temperature. The

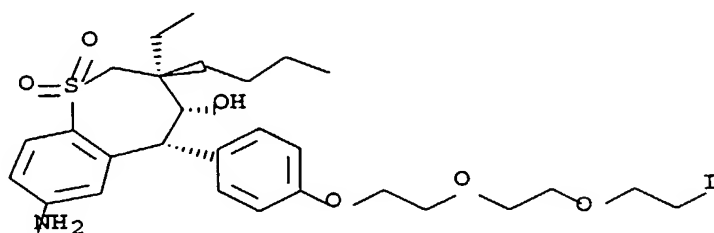
SRL 6071
(C-3021/2)

315

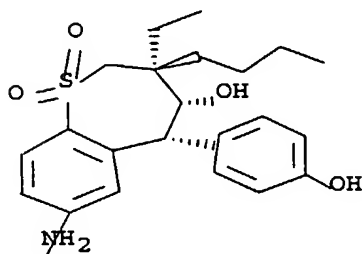
reaction was stirred overnight and the desired product was isolated by removing solvent by rotary evaporation.

Example 63 (Compound No. 295)

5



No. 295



No. 113

10

Sodium Hydride 60% (11 mg, 0.27 mmoles) in 1 cc of acetonitrile at 0 °C was reacted with 0.248 mmoles (.10 g) of Compound No. 54 in 2.5cc of acetonitrile at 0 °C.

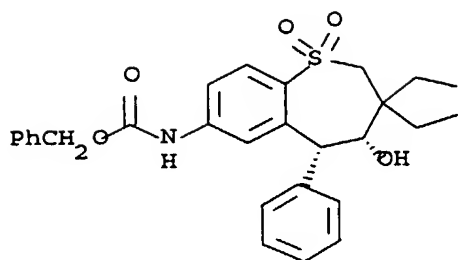
15 Next, 0.(980g 2.48 mmoles) of 1,2-Bis [2-iodoethoxy]ethane]. After warming to room temperature, stir for 14 hours. The product was isolated by column chromatography.

20

Example 64 (Compound No. 286)

SRL 6071
(C-3021/2)

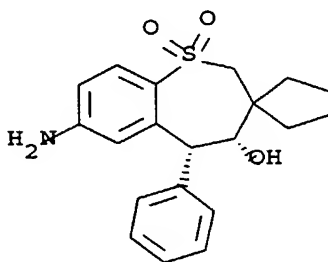
316



No. 286

Following a procedure similar to the one described
in Example 86, *infra* (see Compound No. 118), the title
5 compound was prepared and purified as a colorless
solid; mp 180-181 °C; ¹H NMR (CHCl₃) δ 0.85 (t, J = 6
Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.24-1.42 (m, 2H),
1.46-1.56 (m, 1H), 1.64-1.80 (m, 1H), 2.24-2.38 (m,
1H), 3.15 (AB, J_{AB} = 15 Hz, Δv = 42 Hz, 2H), 4.20 (d, J
10 = 8 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.46 (s, 1H),
6.68 (s, 1H), 7.29-7.51 (m, 10H), 7.74 (d, J = 8 Hz,
1H), 8.06 (d, J = 8 Hz, 1H). FABMS m/z 494 (M+H), HRMS
calcd for (M+H) 494.2001, found 494.1993. Anal. Calcd.
15 for C₂₈H₃₁NO₅S: C, 68.13; H, 6.33; N, 2.84. Found: C,
68.19; H, 6.56; N, 2.74.

Example 65 (Compound No. 287)



No. 287

20

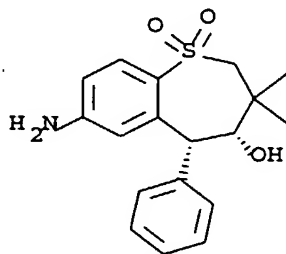
Following a procedure similar to the one described
in Example 89, *infra* (see Compound No. 121), the title
compound was prepared and purified as a colorless

SRL 6071
(C-3021/2)

317

solid: mp 245-246 °C, ^1H NMR (CDCl_3) δ 0.84 (t, J = 6 Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.28, (d, J = 8 Hz, 1H), 1.32-1.42 (m, 1H), 1.48-1.60 (m, 1H), 1.64-1.80 (m, 1H), 2.20-2.36 (m, 1H), 3.09 (AB, J_{AB} = 15 Hz, $\Delta\nu$ = 42 Hz, 2H), 3.97 (bs, 2H), 4.15 (d, J = 8 Hz, 1H), 5.49 (s, 1H), 5.95 (s, 1H), 6.54 (d, J = 7 Hz, 1H), 7.29-7.53 (m, 5H), 7.88 (d, J = 8 Hz, 1H); ESMS 366 ($\text{M}+\text{Li}$).
Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_3\text{S}$: C, 66.82; H, 7.01; N, 3.90.
Found: C, 66.54; H, 7.20; N, 3.69.

Example 66 (Compound No. 288)



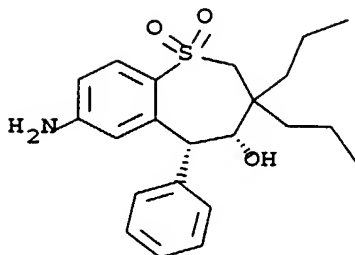
No. 288

Following a procedure similar to the one described in Example 89, *infra* (see Compound No. 121), the title compound was prepared and purified by silica gel chromatography to give the desired product as a colorless solid: mp 185-186°C; ^1H NMR (CDCl_3) δ 1.12 (s, 3H), 1.49 (s, 3H), 3.00 (d, J = 15 Hz, 1H), 3.28 (d, J = 15 Hz, 1H), 4.00 (s, 1H), 5.30 (s, 1H), 5.51 (s, 1H), 5.97 (s, 1H), 6.56 (dd, J = 2.1, 8.4 Hz, 1H), 7.31-7.52 (m, 5H), 7.89 (d, J = 8.4 Hz, 1H). MS (FAB+) ($\text{M}+\text{H}$) m/z 332.

Example 67 (Compound No. 289)

SRL 6071
(C-3021/2)

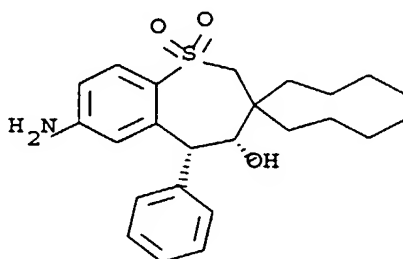
318



No. 289

5 Following a procedure similar to the one described
in Example 89 (see Compound No. 121), the title
compound was prepared and purified by silica gel
chromatography to give the desired product as a white
solid: mp 205-206 °C; ¹H NMR (CDCl₃) δ 0.80-0.95 (m,
6H), 1.10-1.70 (m, 7H), 2.15 (m, 1H), 3.02 (d, J = 15.3
10 Hz, 2H), 3.15 (d, J = 15.1 Hz, 2H), 3.96 (s, br, 2H),
4.14 (d, J = 7.8 Hz, 1H), 5.51 (s, 1H), 5.94 (d, J =
2.2, 1H), 6.54 (dd, J = 8.5, 2.2 Hz, 1H), 7.28-7.50 (m,
6H), 7.87 (d, J = 8.5 Hz, 1H). MS (FAB): m/z 388 (M+H).

15 Example 68 (Compound No. 290)



No. 290

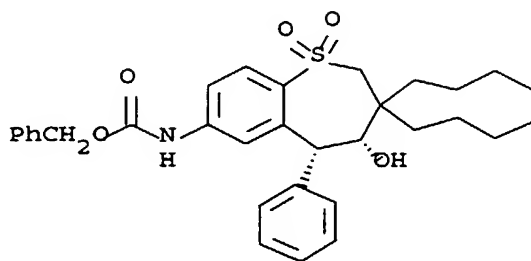
20 Following a procedure similar to the one described
in Example 89, *infra* (see Compound No. 121), the title
compound was prepared and purified as a colorless
solid: mp = 96-98 °C, ¹H NMR (CDCl₃) δ 0.92 (t, J = 7

SRL 6071
(C-3021/2)

319

Hz, 6H), 1.03-1.70 (m, 11H), 2.21 (t, J = 8 Hz, 1H),
3.09 (AB, $J_{AB} = -18$ Hz, $\Delta\nu = 38$ Hz, 2H), 3.96 (bs, 2H),
4.14 (d, J = 7 Hz, 1H), 5.51 (s, 1H), 5.94 (s, 1H),
6.56 (d, J = 9 Hz, 1H), 7.41-7.53 (m, 6H), 7.87 (d, J =
5 8 Hz, 1H); FABMS m/z 416 (M+H).

Example 69



No. 291

10

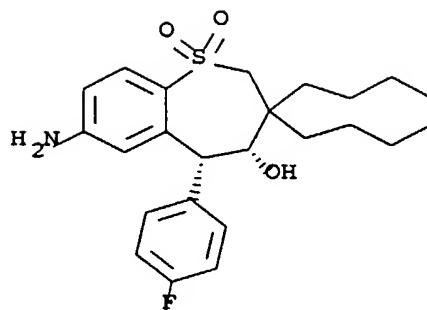
Following a procedure similar to the one described
in Example 86, *infra* (see Compound No. 118), the title
compound was prepared and purified as a colorless
solid: ^1H NMR (CDCl_3) δ 0.91 (t, J = 7 Hz, 6H), 1.02-
15 1.52 (m, 11H), 1.60-1.70 (m, 1H), 2.23 (t, J = 8 Hz,
1H), 3.12 (AB, $J_{AB} = 18$ Hz, $\Delta\nu = 36$ Hz, 2H), 4.18 (d, J
= 7 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.43 (s, 1H),
6.65 (s, 1H), 7.29-7.52 (m, 10H), 7.74 (d, J = 9 Hz,
1H), 8.03 (d, J = 8 Hz, 1H); ESMS m/z 556 (M+Li).

20

Example 70 (Compound No. 292)

SRL 6071
(C-3021/2)

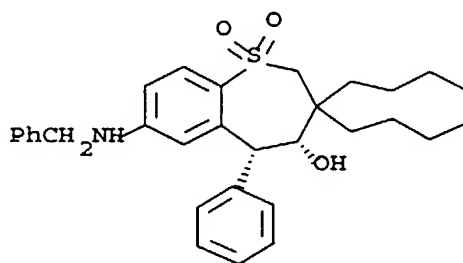
320



No. 292

Following a procedure similar to the one described
in Example 89, *infra* (see Compound No. 121), the title
compound was prepared and purified as a colorless
solid: mp = 111-112.5°C, ^1H NMR (CDCl_3) δ 0.90 (t, J = 8
Hz, 6H), 1.03-1.50 (m, 10H), 1.55-1.70 (m, 2H), 2.18
(t, J = 12 Hz, 2H), 3.07 (AB, J_{AB} = 15 Hz, Δv = 45 Hz,
2H), 4.09 (bs, 2H), 5.49 (s, 1H), 5.91 (s, 1H), 6.55
(d, J = 9 Hz, 1H), 7.10 (t, J = 7 Hz, 2H), 7.46 (t, J =
6 Hz, 2H), 7.87 (d, J = 9 Hz, 1H).

Example 71 (Compound No. 293)



No. 293

During the preparation of Compound No. 290 from
Compound No. 291 using BBr_3 , the title compound was
isolated: ^1H NMR (CDCl_3) δ 0.85 (t, J = 6 Hz, 6H), 0.98-
1.60 (m, 10H), 1.50-1.66 (m, 2H), 2.16 (t, J = 8 Hz,

SRL 6071
(C-3021/2)

321

1H), 3.04 (AB, $J_{AB} = 15$ Hz, $\Delta v = 41$ Hz, 2H), 4.08 (s, 1H), 4.12 (s, 1H), 5.44 (s, 1H), 5.84 (s, 1H), 6.42 (d, $J = 9$ Hz, 1H), 7.12 (d, $J = 8$ Hz, 2H), 7.16-7.26 (m, 10H), 7.83 (d, $J = 8$ Hz, 1H); ESMS m/z 512 (M+Li).

5

Example 72 (Compound No. 294)

Following a procedure similar to the one described in Example 60 (Compound No. 104), the title compound was prepared and purified as a colorless solid: ^1H NMR (CDCl_3) δ 0.90 (t, $J = 6$ Hz, 6H), 1.05-1.54 (m, 9H), 1.60-1.70 (m, 1H), 2.24 (t, $J = 8$ Hz, 1H), 2.80 (s, 6H), 3.05 (AB, $J_{AB} = 15$ Hz, $\Delta v = 42$ Hz, 2H), 4.05-4.18 (m, 2H), 5.53 (s, 1H), 5.93 (s, 1H), 6.94 (d, $J = 9$ Hz, 1H), 7.27-7.42 (m, 4H), 7.45 (d, $J = 8$ Hz, 2H), 7.87 (d, $J = 9$ Hz, 1H); ESMS m/z 444 (M+H).

15

Structures of the compounds of Examples 33 to 72 are shown in Tables 3 and 3A.

20

Examples 73-79, 87, 88 and 91-102

25

Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, compounds were prepared having the structures set forth in Table 3. The starting materials illustrated in the reaction schemes shown above were varied in accordance with principles of organic synthesis well known to the art to introduce the indicated substituents in the 4- and 5- positions (R^3 , R^4 , R^5 , R^6) and in the indicated position on the benzo ring (R^x).

30

Structures of the the compounds produced in Examples 73-102 are set forth in Tables 3 and 3A.

Examples 80-84

SRL 6071
(C-3021/2)

322

Preparation of 115, 116, 111, 113

Preparation of 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.

5 In a 500 ml 2-necked rb flask weigh out 68.3 gms
phosphorus pentachloride (0.328 mole 1.1 eq). Add 50
mls chlorobenzene. Slowly add 60 gms 2-chloro-5-
nitrobenzoic acid (0.298 mole). Stir at room temp
overnight under N₂ then heat 1 hr at 50C.

10 Remove chlorobenzene by high vacuum. Wash residue
with hexane. Dry wt=55.5 gms.

In the same rb flask, dissolve acid chloride (55.5
g 0.25 mole) from above with 100 mls anisole (about 3.4
eq). Chill solution with ice bath while purging with
N₂. Slowly add 40.3g aluminum chloride (1.2 eq 0.3
15 mole). Stir under N₂ for 24 hrs.

After 24 hrs, the solution was poured into 300 mls
1N HCl soln. (cold). Stir this for 15 min. Extract
several times with diethyl ether. Extract organic
layer once with 2% aqueous NaOH then twice with water.

20 Dry organic layer with MgSO₄, dry on vac line. Solid
is washed well with ether and then ethanol before
drying. Wt=34.57g (mixture of meta, ortho and para).

| | Elemental | theory | found |
|----|-----------|--------|-------|
| 25 | C | 57.65 | 57.45 |
| | H | 3.46 | 5.51 |
| | N | 4.8 | 4.8 |
| | Cl | 12.15 | 12.16 |

30 With the next step of the reduction of the ketone
with trifluoromethane sulfonic acid and triethyl silane,
crystallization with ethyl acetate/hexane affords pure
4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.

4-Chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene
was then reacted as specified in the synthesis of 117
35 and 118 from 2-chloro-4-nitrophenylmethane. From these

SRL 6071
(C-3021/2)

323

procedures 115 and 116 can be synthesized. Compounds 111 and 113 can be synthesized from the procedure used to prepare compound 121.

5 Compound 114 can be prepared by reaction of 116 with ethyl mercaptan and aluminum trichloride.

Examples 85 and 86

Preparation of 117 and 118

10 2-Chloro-4-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-4-nitrodiphenylmethane 32. Reaction of 32 with lithium sulfide followed by reacting the resulting sulfide with mesylate IV gives sulfide-aldehyde XXIII.

15 Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIII. Oxidation of XXIII with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 5).

20 The sulfone-aldehyde (31.8 g) was dissolved in ethanol/toluene and placed in a parr reactor with 100 ml toluene and 100 ml of ethanol and 3.2 g of 10% Pd/C and heated to 55 C and 100 psi of hydrogen gas for 14 hours. The reaction was then filtered to remove the catalyst. The amine product (.076 moles, 29.5 g) from this reaction was then reacted with benzyl
25 chloroformate (27.4g) in toluene in the presence of 35 g of potassium carbonate and stirred at room temperature overnight. After work up by extraction with water, the CBZ protected amine product was further purified by precipitation from toluene/hexane.

30 The CBZ protected amine product was then reacted with 3 equivalents of potassium t-butoxide in THF at 0 C to yield compounds 117 and 118 which were separated by silica gel column chromatography.

35 Examples 89 and 90

SRL 6071
(C-3021/2)

324

Preparation of 121 or 122

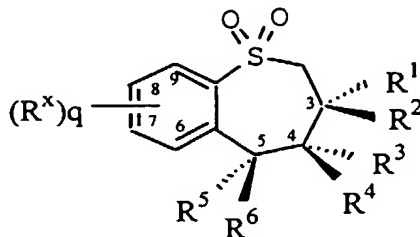
Compound 118 (.013 moles, 6.79g) is dissolved in 135 ml of dry chloroform and cooled to -78 C, next 1.85 ml of boron tribromide (4.9 g) was added and the
5 reaction is allowed to warm to room temperature. Reaction is complete after 1.5 hours. The reaction is quenched by addition of 10% potassium carbonate at 0 C and extract with ether. Removal of ether yields
10 compound 121. A similar procedure can be used to produce 122 from 117.

Examples 93-96

Compounds 126, 127, 128 and 129 as set forth in Table 3 were prepared substantially in the manner
15 described above for compounds 115, 116, 111 and 113, respectively, except that fluorobenzene was used as a starting material in place of anisole.

SRL 6071
(C-3021/2)

325

Table 3: Specific Compounds (#102-111, 113-130, 132-134, 136, 138, 142-144, 262-296)

5

| Cp# | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | (R ^x) _q |
|-----|----------------|----------------|----------------|----------------|---|----------------|---|
| 102 | Et- | n-Bu- | HO- | H- | Ph- | H- | I ⁻ , 7-(CH ₃) ₃ N ⁺ - |
| 103 | n-Bu- | Et- | HO- | H- | Ph- | H- | I ⁻ , 7-(CH ₃) ₃ N ⁺ - |
| 104 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-(CH ₃) ₂ N- |
| 105 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-CH ₃ SO ₂ NH- |
| 106 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-Br-CH ₂ -CONH- |
| 107 | n-Bu- | Et- | HO- | H- | p-n-C ₁₀ H ₂₁ --O-Ph- | H- | 7-NH ₂ - |
| 108 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-C ₅ H ₁₁ CONH- |
| 109 | Et- | n-Bu- | HO- | H- | p-n-C ₁₀ H ₂₁ --O-Ph- | H- | 7-NH ₂ - |
| 110 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-CH ₃ CONH- |
| 111 | n-Bu- | Et- | HO- | H- | p-HO-Ph- | H- | 7-NH ₂ - |
| 113 | Et- | n-Bu- | HO- | H- | p-HO-Ph- | H- | 7-NH ₂ - |

SRL 6071
(C-3021/2)

326

| | | | | | | | |
|-----|-------|-------|-----|----|-------------------------|----|--|
| 114 | Et- | n-Bu- | HO- | H- | p-CH ₃ O-Ph- | H- | 7-NH ₂ - |
| 115 | n-Bu- | Et- | HO- | H- | p-CH ₃ O-Ph- | H- | 7-NH-CBZ |
| 116 | Et- | n-Bu- | HO- | H- | p-CH ₃ O-Ph- | H- | 7-NH-CBZ |
| 117 | n-Bu- | Et- | HO- | H- | Ph- | H- | 7-NH-CBZ |
| 118 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-NH-CBZ |
| 119 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-NHCO ₂ -t-Bu |
| 120 | n-Bu- | Et- | HO- | H- | Ph- | H- | 7-NHCO ₂ -t-Bu |
| 121 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-NH ₂ - |
| 122 | n-Bu- | Et- | HO- | H- | Ph- | H- | 7-NH ₂ - |
| 123 | Et- | n-Bu- | HO- | H- | Ph- | H- | 7-n-C ₆ H ₁₃ -NH- |
| 124 | n-Bu- | Et- | HO- | H- | Ph- | H- | 7-n-C ₆ H ₁₃ -NH- |
| 125 | Et- | n-Bu- | HO- | H- | Ph- | H- | I ⁻ , 8-(CH ₃) ₃ N ⁺ (CH ₂ CH ₂ O) ₃ - |
| 126 | n-Bu- | Et- | HO- | H- | p-F-Ph- | H- | 7-NH-CBZ |
| 127 | n-Bu- | Et- | HO- | H- | p-F-Ph- | H- | 7-NH ₂ - |
| 128 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-NH-CBZ |
| 129 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-NH ₂ - |
| 130 | Et- | n-Bu- | HO- | H- | Ph- | H- | I ⁻ , 8-(CH ₃) ₃ N ⁺ C ₆ H ₁₂ O- |
| 132 | Et- | n-Bu- | HO- | H- | Ph- | H- | 8-phthalimidyl-C ₆ H ₁₂ O- |

SRL 6071
(C-3021/2)

327

| | | | | | | | |
|-----|-------|-------|-----|-----|-------------------------|-------------------------|---|
| 133 | Et- | n-Bu- | HO- | H- | Ph- | H- | 8-n- C ₁₀ H ₂₁ - |
| 134 | Et- | n-Bu- | HO- | H- | Ph- | H- | 8- I- (C ₂ H ₄ O) 3- |
| 136 | Et- | n-Bu- | HO- | H- | Ph- | H- | 8- HO- |
| 138 | n-Bu- | Et- | HO- | H- | Ph- | H- | 8- CH ₃ CO ₂ - |
| 142 | Et- | n-Bu- | H- | HO- | H- | m-CH ₃ O-Ph- | 7-CH ₃ S- |
| 143 | Et- | n-Bu- | HO- | H- | m-CH ₃ O-Ph- | H- | 7-CH ₃ S- |
| 144 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-(N)- azetidine |
| 262 | Et- | n-Bu- | HO- | H- | m-CH ₃ O-Ph- | H- | 7-CH ₃ O- |
| 263 | Et- | n-Bu- | H- | HO- | H- | m-CH ₃ O-Ph- | 7-CH ₃ O- |
| 264 | Et- | n-Bu- | HO- | H- | m-CF ₃ -Ph- | H- | 7-CH ₃ O- |
| 265 | Et- | n-Bu- | H- | HO- | H- | m-CF ₃ -Ph- | 7-CH ₃ O- |
| 266 | Et- | n-Bu- | HO- | H- | m-HO-Ph- | H- | 7-HO- |
| 267 | Et- | n-Bu- | HO- | H- | m-HO-Ph- | H- | 7-CH ₃ O- |
| 268 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-CH ₃ O- |
| 269 | Et- | n-Bu- | H- | HO- | H- | p-F-Ph- | 7-CH ₃ O- |
| 270 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-HO- |
| 271 | Et- | n-Bu- | HO- | H- | m-CH ₃ O-Ph- | H- | 7-Br- |
| 272 | Et- | n-Bu- | H- | HO- | H- | m-CH ₃ O-Ph- | 7-Br- |
| 273 | Et- | n-Bu- | H- | HO- | H- | p-F-Ph- | 7-F- |

SRL 6071
(C-3021/2)

328

| | | | | | | | |
|-----|---------------------------------------|---------------------------------------|-----|-----|-------------------------|-------------------------|--------------------------------------|
| 274 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-F- |
| 275 | Et- | n-Bu- | H- | HO- | H- | m-CH ₃ O-Ph- | 7-F- |
| 276 | Et- | n-Bu- | HO- | H- | m-CH ₃ O-Ph- | H- | 7-F- |
| 277 | Et- | n-Bu- | HO- | H- | m-F-Ph- | H- | 7-CH ₃ O- |
| 278 | Et- | n-Bu- | H- | HO- | H- | o-F-Ph- | 7-CH ₃ O- |
| 279 | Et- | n-Bu- | H- | HO- | H- | m-F-Ph- | 7-CH ₃ O- |
| 280 | Et- | n-Bu- | HO- | H- | o-F-Ph- | H- | 7-CH ₃ O- |
| 281 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-CH ₃ S- |
| 282 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-CH ₃ - |
| 283 | Et- | n-Bu- | H- | HO- | H- | p-F-Ph- | 7-CH ₃ - |
| 284 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-(N)- morpholine |
| 285 | Et- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-(N)- pyrroli- dine |
| 286 | Et- | Et- | HO- | H- | Ph- | H- | 7-NH-CBZ- |
| 287 | Et- | Et- | HO- | H- | Ph- | H- | 7-NH ₂ - |
| 288 | CH ₃ - | CH ₃ - | HO- | H- | Ph- | H- | 7-NH ₂ - |
| 289 | n- C ₃ H ₇ - | n- C ₃ H ₇ - | HO- | H- | Ph- | H- | 7-NH ₂ - |
| 290 | n-Bu- | n-Bu- | HO- | H- | Ph- | H- | 7-NH ₂ - |
| 291 | n-Bu- | n-Bu- | HO- | H- | Ph- | H- | 7-NH-CBZ- |
| 292 | n-Bu- | n-Bu- | HO- | H- | p-F-Ph- | H- | 7-NH ₂ - |
| 293 | n-Bu- | n-Bu- | HO- | H- | Ph- | H- | 7-PhCH ₂ N- |
| 294 | n-Bu- | n-Bu- | HO- | H- | Ph- | H- | 7-(CH ₃) ₂ N- |

SRL 6071
(C-3021/2)

329

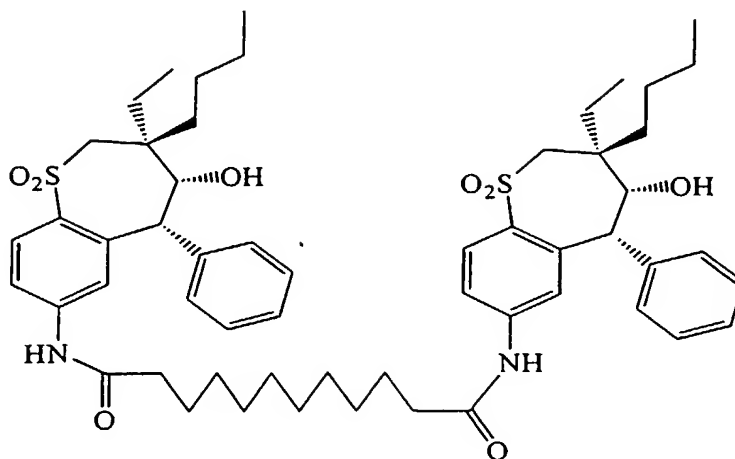
| | | | | | | | |
|-----|-----|-------|-----|----|--|----|---------------------|
| 295 | Et- | n-Bu- | HO- | H- | p-I- (C ₂ H ₄ O) ₃ - Ph- | H- | 7-NH ₂ - |
| 296 | Et- | n-Bu- | HO- | H- | I ⁻ , p- (CH ₃) ₃ N ⁺ (C 2H ₄ O) ₃ -Ph- | H- | 7-NH ₂ - |

SRL 6071
(C-3021/2)

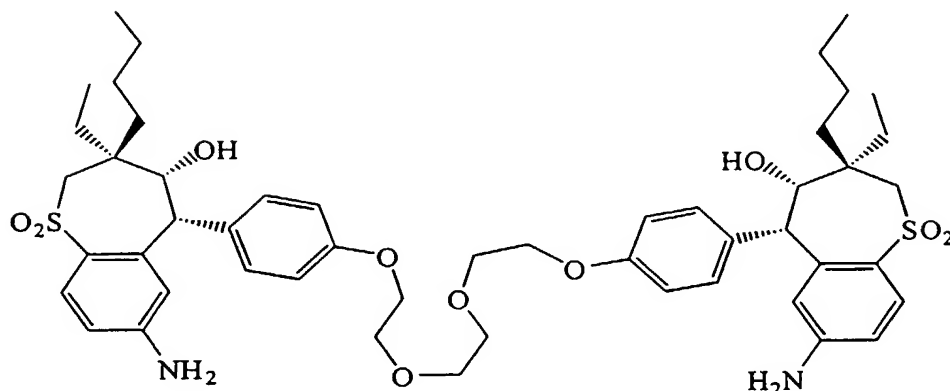
330

TABLE 3A

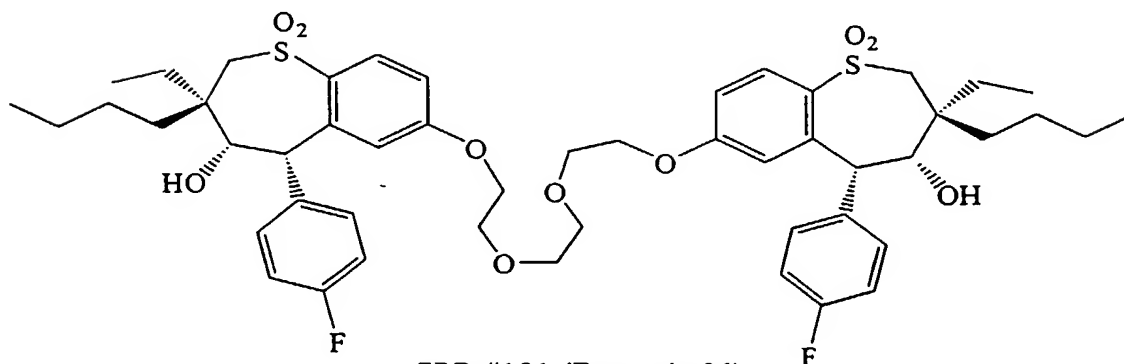
Bridged Benzothiepines (#101, 112, 131, 135, 137, 139-141)



CPD # 101 (Example 59)



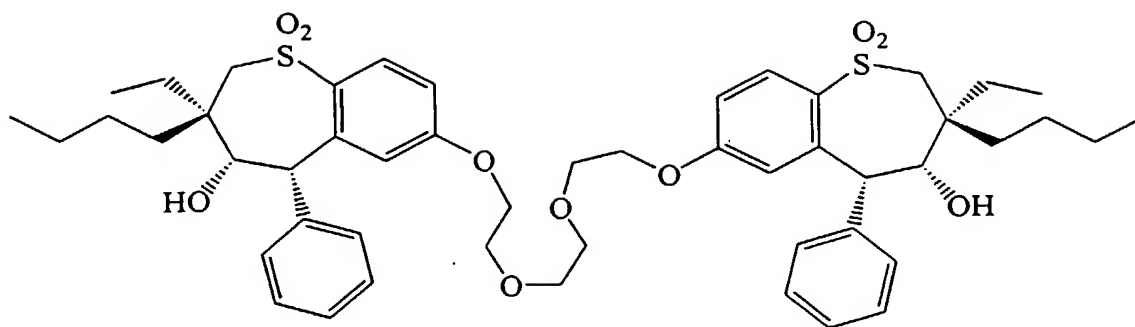
CPD # 112 (Example 53)



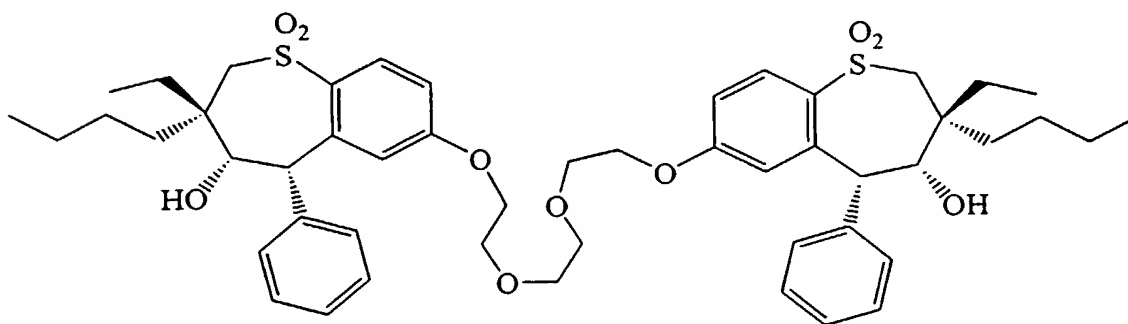
CPD # 131 (Example 56)

SRL 6071
(C-3021/2)

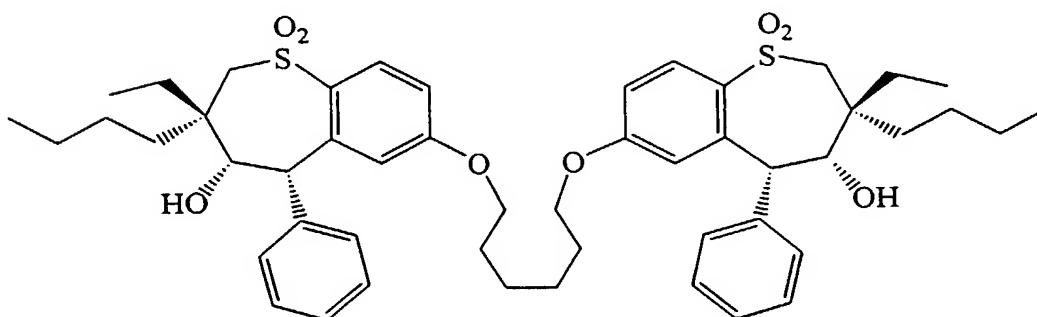
331



CPD #135 (Example 55)



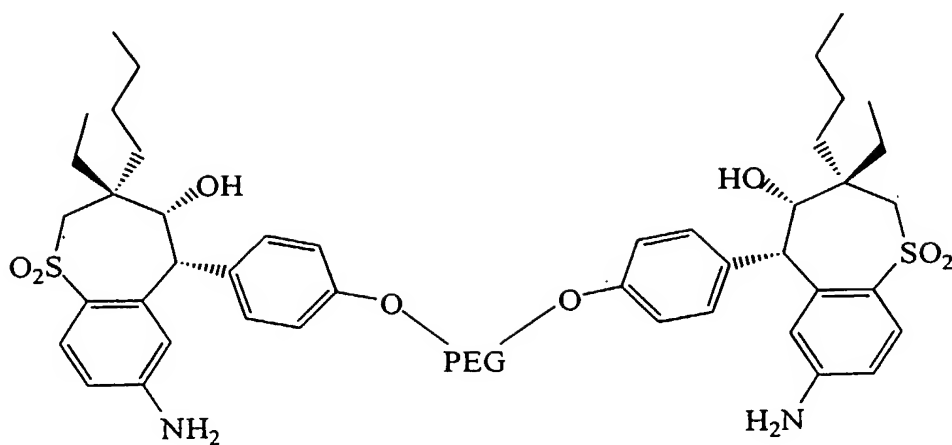
CPD #137 (Example 57)



CPD #139 (Example 58)

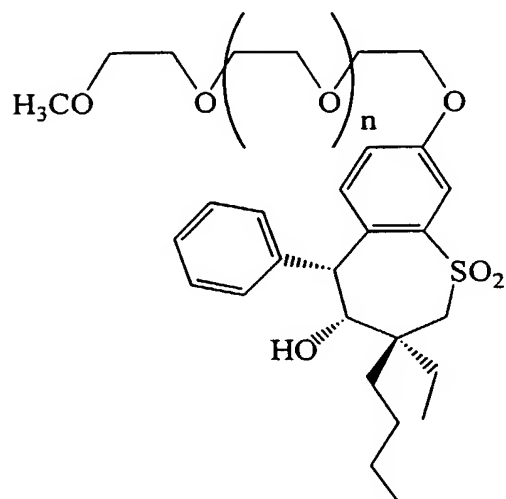
SRL 6071
(C-3021/2)

332



PEG = 3400 molecular weight polyethyleneglycol bridge

CPD #140 (Example 51)



CPD #141 (Example 50)

SRL 6071
(C-3021/2)

333

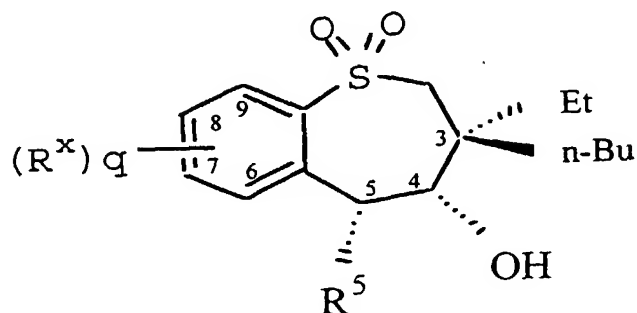
Examples 104-231

5 Using in each instance a method generally
described in those of Examples 1 to 72 appropriate to
the substituents to be introduced, including where
necessary other common synthesis expedients well known
to the art, compounds are prepared having the
structures set forth in Table 4. The starting
materials illustrated in the reaction schemes shown
above are varied in accordance with principles of
10 organic synthesis well known to the art in order to
introduce the indicated substituents in the 4- and 5-
positions (R^3 , R^4 , R^5 , R^6) and in the indicated position
on the benzo ring (R^x).

SRL 6071
(C-3021/2)

334

Table 4: Alternative compounds #1 (#302-312, 314-430)



| Cpd# | R ⁵ | (R ^x) q |
|------|-------------------------|--|
| 302 | p-F-Ph- | 7-(1-aziridine) |
| 303 | p-F-Ph- | 7-EtS- |
| 304 | p-F-Ph- | 7-CH ₃ S(O)- |
| 305 | p-F-Ph- | 7-CH ₃ S(O) ₂ - |
| 306 | p-F-Ph- | 7-PhS- |
| 307 | p-F-Ph- | 7-CH ₃ S- 9-CH ₃ S- |
| 308 | p-F-Ph- | 7-CH ₃ O- 9-CH ₃ O- |
| 309 | p-F-Ph- | 7-Et- |
| 310 | p-F-Ph- | 7-iPr- |
| 311 | p-F-Ph- | 7-t-Bu- |
| 312 | p-F-Ph- | 7-(1-pyrazole)- |
| 314 | m-CH ₃ O-Ph | 7-(1-azetidine) |
| 315 | m-CH ₃ O-Ph- | 7-(1-aziridine) |
| 316 | m-CH ₃ O-Ph- | 7-EtS- |
| 317 | m-CH ₃ O-Ph- | 7-CH ₃ S(O)- |

SRL 6071
(C-3021/2)

335

| | | |
|-----|-------------------------|--|
| 318 | m-CH ₃ O-Ph- | 7-CH ₃ S(O) ₂ - |
| 319 | m-CH ₃ O-Ph- | 7-PhS- |
| 320 | m-CH ₃ O-Ph | 7-CH ₃ S- 9-CH ₃ S- |
| 321 | m-CH ₃ O-Ph | 7-CH ₃ O- 9-CH ₃ O- |
| 322 | m-CH ₃ O-Ph | 7-Et- |
| 323 | m-CH ₃ O-Ph | 7-iPr- |
| 324 | m-CH ₃ O-Ph | 7-t-Bu- |
| 325 | p-F-Ph- | 6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O- |
| 326 | p-F-Ph- | 7-(1-azetidine) 9-CH ₃ - |
| 327 | p-F-Ph- | 7-EtS- 9-CH ₃ - |
| 328 | p-F-Ph- | 7-CH ₃ S(O)- 9-CH ₃ - |
| 329 | p-F-Ph- | 7-CH ₃ S(O) ₂ - 9-CH ₃ - |
| 330 | p-F-Ph- | 7-PhS- 9-CH ₃ - |
| 331 | p-F-Ph- | 7-CH ₃ S- 9-CH ₃ - |
| 332 | p-F-Ph- | 7-CH ₃ O- 9-CH ₃ - |
| 333 | p-F-Ph- | 7-CH ₃ - 9-CH ₃ - |
| 334 | p-F-Ph- | 7-CH ₃ O- 9-CH ₃ O- |

SRL 6071
(C-3021/2)

336

| | | |
|-----|-------------------------|--|
| 335 | p-F-Ph- | 7-(1-pyrrole) |
| 336 | p-F-Ph- | 7-(N)N'-methylpiperazine |
| 337 | p-F-Ph- | Ph- |
| 338 | p-F-Ph- | 7-CH ₃ C(=CH ₂)- |
| 339 | p-F-Ph- | 7-cyclpropyl |
| 340 | p-F-Ph- | 7-(CH ₃) ₂ NHN- |
| 341 | p-F-Ph- | 7-(N)-azetidine 9-CH ₃ S- |
| 342 | p-F-Ph- | 7-(N-pyrrolidine) 9-CH ₃ S- |
| 343 | p-F-Ph- | 7-(CH ₃) ₂ N- 9-CH ₃ S- |
| 344 | m-CH ₃ O-Ph- | 7-(1-pyrazole) |
| 345 | m-CH ₃ O-Ph- | 7-(N)N'-methylpiperazine |
| 346 | m-CH ₃ O-Ph- | Ph- |
| 347 | m-CH ₃ O-Ph- | 7-CH ₃ C(=CH ₂)- |
| 348 | m-CH ₃ O-Ph- | 7-cyclopropyl |
| 349 | m-CH ₃ O-Ph- | 7-(CH ₃) ₂ NHN- |
| 350 | m-CH ₃ O-Ph- | 7-(N)-azetidine 9-CH ₃ S- |
| 351 | m-CH ₃ O-Ph- | 7-(N-pyrrolidine)- 9-CH ₃ S- |
| 352 | m-CH ₃ O-Ph- | 7-(CH ₃) ₂ N- 9-CH ₃ S- |

SRL 6071
(C-3021/2)

337

| | | |
|-----|-------------------------|--|
| 353 | m-CH ₃ O-Ph- | 6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O- |
| 354 | m-CH ₃ O-Ph- | 7-(1-azetidine) 9-CH ₃ - |
| 355 | m-CH ₃ O-Ph- | 7-EtS- 9-CH ₃ - |
| 356 | m-CH ₃ O-Ph- | 7-CH ₃ S(O)- 9-CH ₃ - |
| 357 | m-CH ₃ O-Ph- | 7-CH ₃ S(O) ₂ - 9-CH ₃ - |
| 358 | m-CH ₃ O-Ph- | 7-PhS- 9-CH ₃ - |
| 359 | m-CH ₃ O-Ph- | 7-CH ₃ S- 9-CH ₃ - |
| 360 | m-CH ₃ O-Ph- | 7-CH ₃ O- 9-CH ₃ - |
| 361 | m-CH ₃ O-Ph- | 7-CH ₃ - 9-CH ₃ - |
| 362 | m-CH ₃ O-Ph- | 7-CH ₃ O- 9-CH ₃ O- |
| 363 | thien-2-yl | 7-(1-aziridine) |
| 364 | thien-2-yl | 7-EtS- |
| 365 | thien-2-yl | 7-CH ₃ S(O)- |
| 366 | thien-2-yl | 7-CH ₃ S(O) ₂ - |
| 367 | thien-2-yl | 7-PhS- |
| 368 | thien-2-yl | 7-CH ₃ S- 9-CH ₃ S- |
| 369 | thien-2-yl | 7-CH ₃ O- 9-CH ₃ O- |

SRL 6071
(C-3021/2)

338

| | | |
|-----|-----------------|--|
| 370 | thien-2-yl | 7-Et- |
| 371 | thien-2-yl | 7-iPr- |
| 372 | thien-2-yl | 7-t-Bu- |
| 373 | thien-2-yl | 7-(1-pyrrole)- |
| 374 | thien-2-yl | 7-CH ₃ O- |
| 375 | thien-2-yl | 7-CH ₃ S- |
| 376 | thien-2-yl | 7-(1-azetidine) |
| 377 | thien-2-yl | 7-Me- |
| 378 | 5-Cl-thien-2-yl | 7-(1-azetidine) |
| 379 | 5-Cl-thien-2-yl | 7-(1-aziridine) |
| 380 | 5-Cl-thien-2-yl | 7-EtS- |
| 381 | 5-Cl-thien-2-yl | 7-CH ₃ S(O)- |
| 382 | 5-Cl-thien-2-yl | 7-CH ₃ S(O) ₂ - |
| 383 | 5-Cl-thien-2-yl | 7-PhS- |
| 384 | 5-Cl-thien-2-yl | 7-CH ₃ S- 9-CH ₃ S- |
| 385 | 5-Cl-thien-2-yl | 7-CH ₃ O- 9-CH ₃ O- |
| 386 | 5-Cl-thien-2-yl | 7-Et- |
| 387 | 5-Cl-thien-2-yl | 7-iPr- |
| 388 | 5-Cl-thien-2-yl | 7-t-Bu- |
| 389 | 5-Cl-thien-2-yl | 7-CH ₃ O- |
| 390 | 5-Cl-thien-2-yl | 7-CH ₃ S- |
| 391 | 5-Cl-thien-2-yl | 7-Me |

SRL 6071
(C-3021/2)

339

| | | |
|-----|------------|--|
| 392 | thien-2-yl | 7-(1-azetidine) 9-CH ₃ - |
| 393 | thien-2-yl | 7-EtS- 9-CH ₃ - |
| 394 | thien-2-yl | 7-CH ₃ S(O)- 9-CH ₃ - |
| 395 | thien-2-yl | 7-CH ₃ S(O) ₂ - 9-CH ₃ - |
| 396 | thien-2-yl | 7-PhS- 9-CH ₃ - |
| 397 | thien-2-yl | 7-CH ₃ S- 9-CH ₃ - |
| 398 | thien-2-yl | 7-CH ₃ O- 9-CH ₃ - |
| 399 | thien-2-yl | 7-CH ₃ - 9-CH ₃ - |
| 400 | thien-2-yl | 7-CH ₃ O- 9-CH ₃ O- |
| 401 | thien-2-yl | 7-(1-pyrazrole) |
| 402 | thien-2-yl | 7-(N)N'-methylpiperazine |
| 403 | thien-2-yl | Ph- |
| 404 | thien-2-yl | 7-CH ₃ C(=CH ₂)- |
| 405 | thien-2-yl | 7-cyclpropyl |
| 406 | thien-2-yl | 7-(CH ₃) ₂ NHN- |
| 407 | thien-2-yl | 7-(N)-azetidine 9-CH ₃ S- |
| 408 | thien-2-yl | 7-(N-pyrrolidine) 9-CH ₃ S- |
| 409 | thien-2-yl | 7-(CH ₃) ₂ N- 9-CH ₃ S- |

SRL 6071
(C-3021/2)

340

| | | |
|-----|-----------------|--|
| 411 | 5-Cl-thien-2-yl | 7-(1-pyrazrole) |
| 412 | 5-Cl-thien-2-yl | 7-(N)N'-methylpiperazine |
| 413 | 5-Cl-thien-2-yl | Ph- |
| 414 | 5-Cl-thien-2-yl | 7-CH ₃ C(=CH ₂)- |
| 415 | 5-Cl-thien-2-yl | 7-cyclopropyl |
| 416 | 5-Cl-thien-2-yl | 7-(CH ₃) ₂ NHN- |
| 417 | 5-Cl-thien-2-yl | 7-(N)-azetidine 9-CH ₃ S- |
| 418 | 5-Cl-thien-2-yl | 7-(N-pyrrolidine)- 9-CH ₃ S- |
| 419 | 5-Cl-thien-2-yl | 7-(CH ₃) ₂ N- 9-CH ₃ S- |
| 420 | 5-Cl-thien-2-yl | 7-(1-azetidine) 9-CH ₃ - |
| 421 | 5-Cl-thien-2-yl | 7-EtS- 9-CH ₃ - |
| 422 | 5-Cl-thien-2-yl | 7-CH ₃ S(O)- 9-CH ₃ - |
| 423 | 5-Cl-thien-2-yl | 7-CH ₃ S(O) ₂ - 9-CH ₃ - |
| 424 | 5-Cl-thien-2-yl | 7-PhS- 9-CH ₃ - |
| 425 | 5-Cl-thien-2-yl | 7-CH ₃ S- 9-CH ₃ - |
| 426 | 5-Cl-thien-2-yl | 7-CH ₃ O- 9-CH ₃ - |

SRL 6071
(C-3021/2)

341

| | | |
|-----|-----------------|--|
| 427 | 5-Cl-thien-2-yl | 7-CH ₃ - 9-CH ₃ - |
| 428 | 5-Cl-thien-2-yl | 7-CH ₃ O- 9-CH ₃ O- |
| 429 | thien-2-yl | 6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O- |
| 430 | 5-Cl-thien-2-yl | 6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O- |

Examples 232-1394

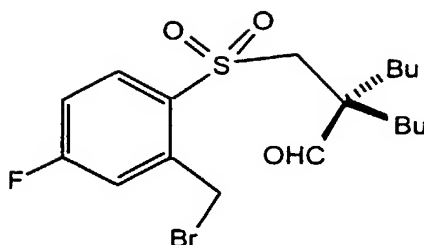
Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 1. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5-positions (R³, R⁴, R⁵, R⁶) and in the indicated position on the benzo ring (R^x).

Example 1395

Dibutyl 4-fluorobenzene dialdehyde

SRL 6071
(C-3021/2)

342



Step 1: Preparation of dibutyl 4-fluoro benzene dialdehyde

5 To a stirred solution of 17.5 g (123 mmol) of 2,5-difluorobenzaldehyde (Aldrich) in 615 mL of DMSO at ambient temperature was added 6.2 g (135 mmol) of lithium sulfide (Aldrich). The dark red solution was stirred at 75 C for 1.5 hours, or until the starting material was completely consumed, and then 34 g (135 mmol) of dibutyl mesylate aldehyde was added at about 10 50 C. The reaction mixture was stirred at 75 C for three hours or until the reaction was completed. The cooled solution was poured into water and extracted with ethyl acetate. The combined extracts were washed with water several times, dried (MgSO₄) and 15 concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 23.6 g (59%) of fluorobenzene dialdehyde as a yellow oil: ¹H NMR 20 (CDCl₃) δ 0.87 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.78 (m, 4H), 3.09 (s, 2H), 7.2-7.35 (m, 1H), 7.5-7.6 (m, 2H), 9.43 (s, 1H), 10.50 (d, J = 2.62 Hz, 1H).

Step 2: Preparation of dibutyl 4-fluorobenzyl alcohol

25 To a solution of 22.6 g (69.8 mmol) of the dialdehyde obtained from Step 1 in 650 mL of THF at -60 C was added 69.8 mL (69.8 mmol) of DIBAL (1M in THF) via a syringe. The reaction mixture was stirred at -40 C for 20 hours. To the cooled solution at -40 C was added 30 sufficient amount of ethyl acetate to quench the excess

SRL 6071
(C-3021/2)

343

of DIBAL, followed by 3 N HCl. The mixture was extracted with ethyl acetate, washed with water, dried (MgSO₄), and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave
5 13.5 g (58%) of recovered starting material, and 8.1 g (36%) of the desired fluorobenzyl alcohol as a colorless oil: ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.72 (m, 4H), 1.94 (br s, 1H), 3.03 (s, 2H), 4.79 (s, 2H), 6.96 (dt, J = 8.46,
10 3.02 Hz, 1H), 7.20 (dd, J = 9.47, 2.82 Hz, 1H), 7.42 (dd, J = 8.67, 5.64, 1H), 9.40 (s, 1H).

Step 3: Preparation of dibutyl 4-fluorobenzyl bromide
To a solution of 8.1 g (25 mmol) of benzyl alcohol
15 obtained from Step 2 in 100 mL of DMF at -40 C was added 47 g (50 mmol) of bromotriphenylphosphonium bromide (Aldrich). The resulting solution was stirred cold for 30 min, then was allowed to warm to 0 C. To the mixture was added 10% solution of sodium sulfite
20 and ethyl acetate. The extract was washed a few times with water, dried (MgSO₄), and concentrated in vacuo. The mixture was stirred in small amount of ethyl acetate/hexane mixture (1:4 ratio) and filtered through a pad of silica gel, eluting with same solvent mixture.
25 The combined filtrate was concentrated in vacuo to give 9.5 g (98%) of the desired product as a colorless oil: ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.55-1.78 (m, 4H), 3.11 (s, 2H), 4.67 (s, 2H), 7.02 (dt, J = 8.46, 3.02 Hz, 1H), 7.15 (dd, J = 9.47,
30 2.82 Hz, 1H), 7.46 (dd, J = 8.67, 5.64, 1H), 9.45 (s, 1H).

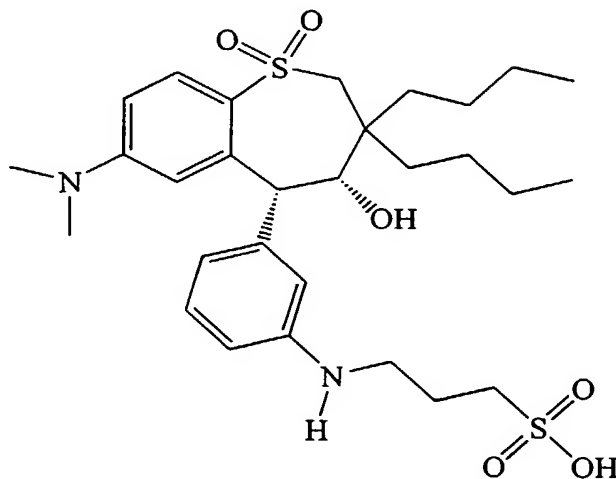
Step 4: Preparation of sulfonyl 4-fluorobenzyl bromide

SRL 6071
(C-3021/2)

344

To a solution of 8.5 g (25 mmol) of sulfide obtained from Step 3 in 200 mL of CH_2Cl_2 at 0 $^\circ\text{C}$ was added 15.9 g (60 mmol) of mCPBA (64% peracid). The resulting solution was stirred cold for 10 min, then was allowed to stirred ambient temperature for 5 hours. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed several times with saturated Na_2CO_3 , dried (MgSO_4), and concentrated in vacuo to give 10.2 g (98%) of the desired product as a colorless oil: ^1H NMR (CDCl_3) δ 0.91 (t, $J = 7.05$ Hz, 6H), 1.03-1.4 (m, 8H), 1.65-1.82 (m, 2H), 1.90-2.05 (m, 2H), 3.54 (s, 2H), 5.01 (s, 2H), 7.04-7.23 (m, 1H), 7.30 (dd, $J = 8.87, 2.42$ Hz, 1H), 8.03 (dd, $J = 8.86, 5.64$, 1H), 9.49 (s, 1H).

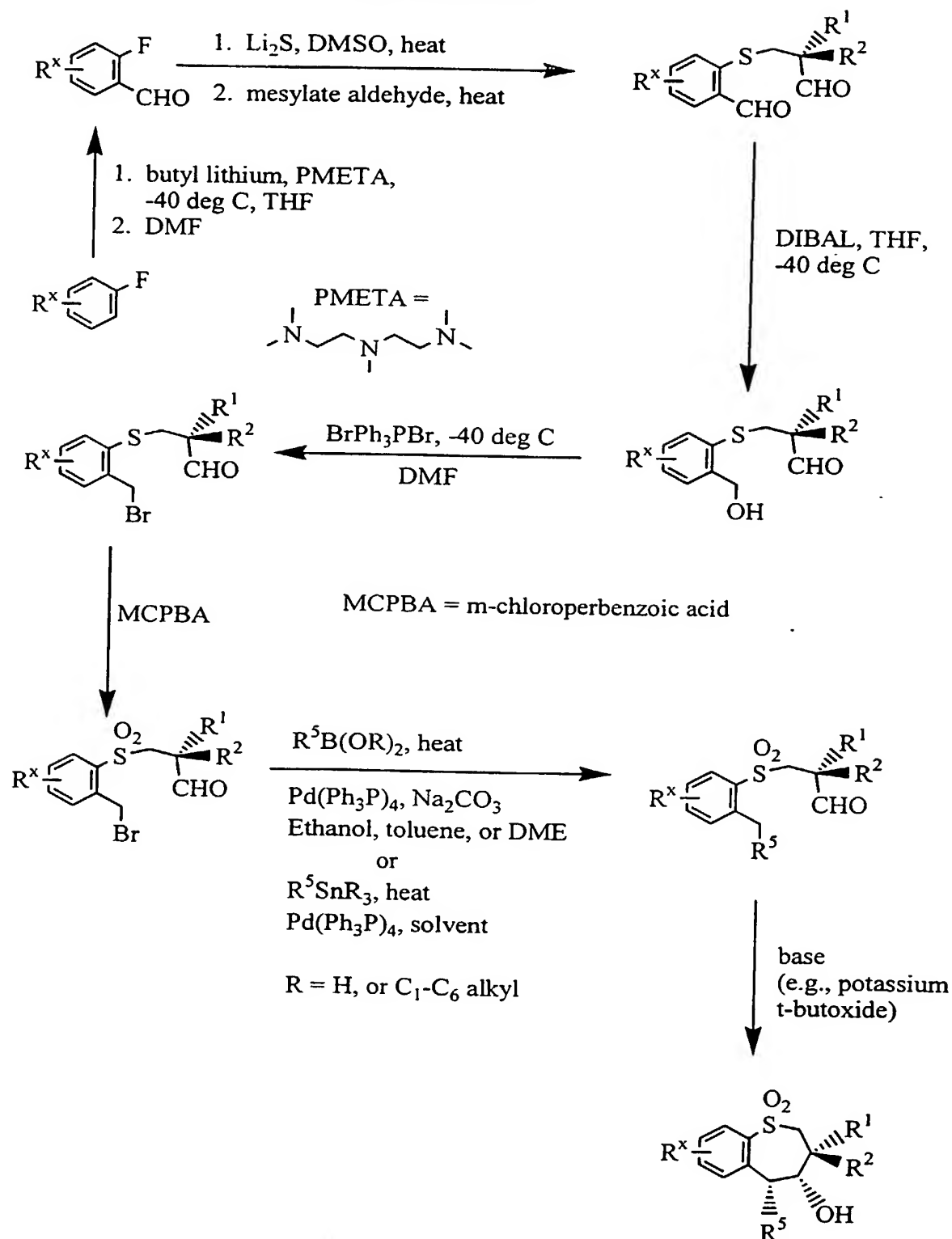
Example 1396



SRL 6071
(C-3021/2)

345

Generic Scheme X



SRL 6071
(C-3021/2)

346

Generic Scheme X: The nucleophilic substitution of an appropriately substituted 2-fluorobenzaldehyde with lithium sulfide or other nucleophilic sulfide anion in polar solvent (such as DMF, DMA, DMSO .etc), followed by the addition of dialkyl mesylate aldehyde (X), provided a dialkyl benzene dialdehyde Y. DIBAL reduction of the dialdehyde at low temperature yielded benzyl alcohol monoaldehyde Z. Conversion of benzyl alcohol to benzyl bromide, followed by oxidation of sulfide to sulfone yielded the key intermediate W.

15 Preparation of N-propylsulfonic acid

To a solution of 51 mg (111 μ m) Compound X in ethanol (400 μ l) was added 1,3 propane sultone (19.5 μ l, 222 μ m). The reaction was stirred in a sealed vial at 55 °C for 25 hr. Sample was concentrated under a nitrogen stream and purified by reversed phase chromatography using acetonitrile/water as eluent (30-45%) and afforded the desired material as an off-white solid (28.4 mg, 44%): ^1H NMR (CDCl_3) δ 0.82-0.96 (m, 6H), 1.11-1.52 (m of m, 10H), 1.58-1.72 (m, 1H), 2.08-2.21 (m, 1H), 2.36-2.50 (m, 2H), 2.93 (s, 6H), 3.02-3.22 (m of m, 5H), 3.58-3.76 (m, 2H), 4.15 (s, 1H), 5.51 (s, 1H), 6.45-6.58 (m, 1H), 6.92-7.02 (m, 1H), 7.35-7.41 (m, 1H), 7.41-7.51 (m, 2H), 8.08 (d, $J = 8.1$ Hz, 1H), 8.12-8.25 (m, 1H); MS ES- M-H m/z 579.

30 Example 1397

35 The 7-fluoro, 9-fluoro and 7,9-difluoro analogs of benzothiepine compounds of this invention can be

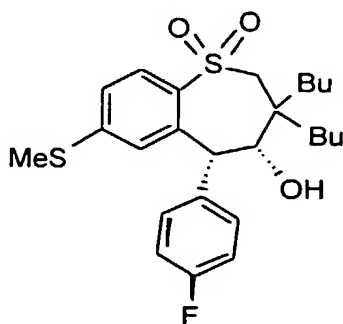
SRL 6071
(C-3021/2)

347

reacted with sulfur and nitrogen nucleophiles to give the corresponding sulfur and nitrogen substituted analogs. The following example demonstrates the synthesis of these analogs.

5

3,3-Dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.



10

A mixture of 0.4 g of 3,3-dibutyl-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by previously described method, 0.12 g of sodium methanethiolate and 20 ml of DMF was stirred at 50 C for 3 days. An additional 0.1 g of sodium methanethiolate was added to the reaction mixture and the mixture was stirred for additional 20 h at 50 C then was concentrated in vacuo. The residue was triturated with water and extracted with ether. The ether extract was dried over MgSO_4 and concentrated in vacuo to 0.44 g of an oil. Purification by HPLC (10% EtOAc in hexane) gave 0.26 g of needles, mp 164-165.5 °C.

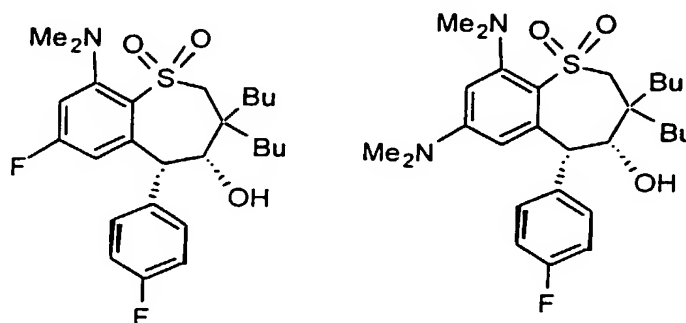
25

3,3-Dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide and 7,9-

SRL 6071
(C-3021/2)

348

Bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.



5

A solution of 0.105 g of 3,3-dibutyl-7,9-difluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by the method described previously, in 20 ml of 2 N dimethylamine in THF was heated at 160 C in a sealed Parr reactor overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with 25 ml of water and extracted with ether. The ether extract was dried over MgSO_4 and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc in hexane) to give 35 mg of an earlier fraction which was identified as 3,3-dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 480 ($\text{M}^+ + 1$), and 29 mg of a later fraction which was identified as 7,9-bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 505 ($\text{M}^+ + 1$).

25

The compounds of this invention can also be synthesized using cyclic sulfate (XL, below) as the

SRL 6071
(C-3021/2)

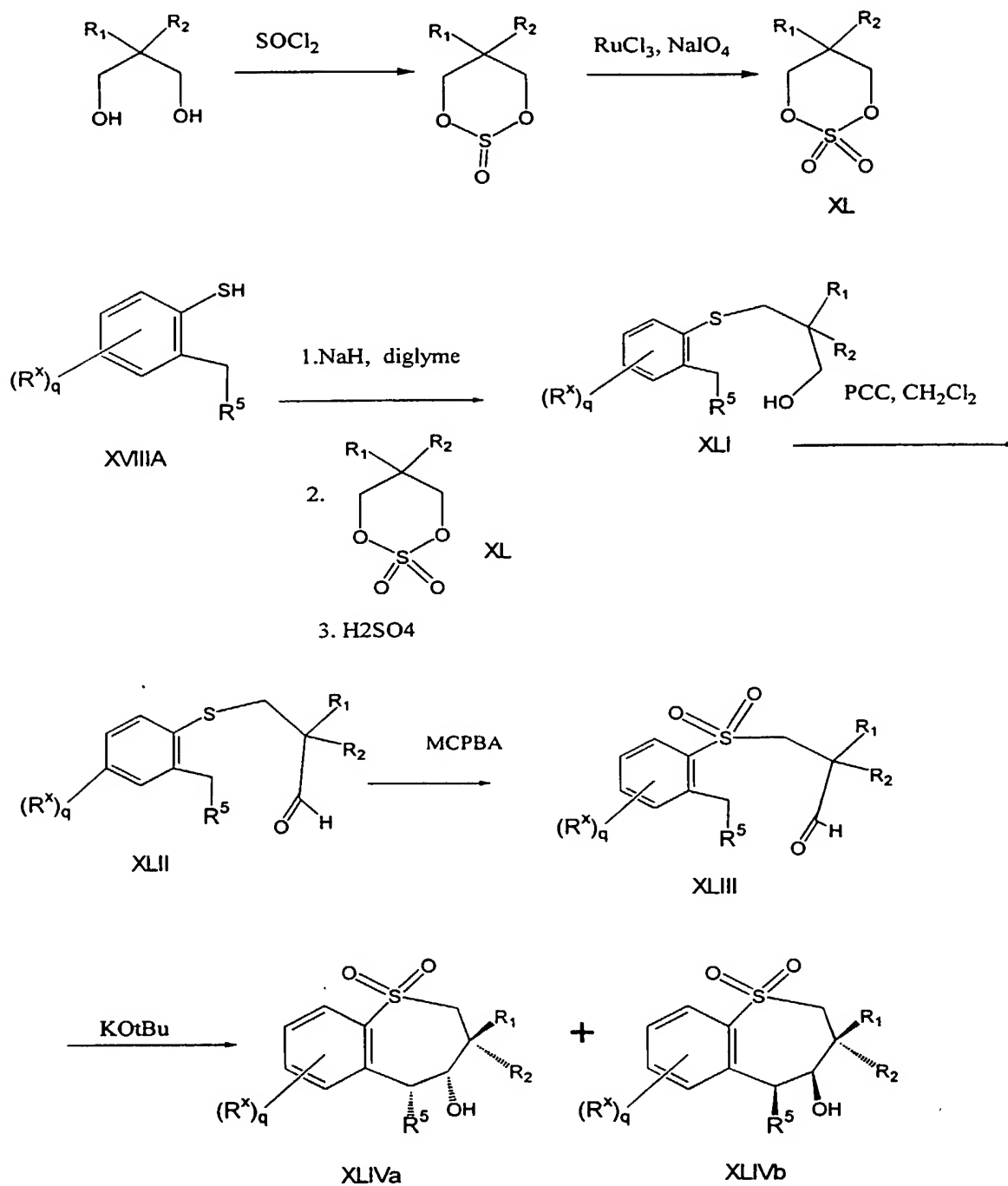
349

reagent as shown in the following schemes XI and XII.
The following examples describe a procedure for using
the cyclic sulfate as the reagent.

SRL 6071
(C-3021/2)

350

SCHEME XI.

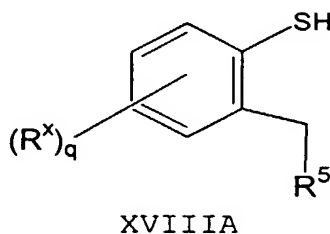


SRL 6071
(C-3021/2)

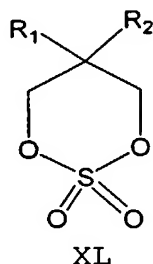
351

benzothiepine-1,1-dioxides, particularly 3,3-dialkyl
analogs, starting from the thiophenol XVIIIA.
Thiophenol XVIIIA can be reacted with cyclic sulfate XL
to give the alcohol XLI which can be oxidized to yield
the aldehyde XLII. Aldehyde XLII itself can be further
oxidized to give the sulfone XLIII which can be
cyclized to give a stereoisomeric mixture of
benzothiepine XLIVa and XLIVb.

Thiophenol XVIIIA can be prepared according to
Scheme 3 as previously discussed and has the following
formula:



wherein R^5 , R^x and q are as previously defined for the
compounds of formula I. Cyclic sulfate XL can be
prepared according to synthetic procedures known in the
art and has the following formula:



wherein R^1 and R^2 are as previously defined for the
compounds of formula I. Preferably, R^1 and R^2 are
alkyl; more preferably, they are selected from the
group consisting of methyl, ethyl, propyl, isopropyl,
n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl;
and still more preferably, R^1 and R^2 are n-butyl.

In the process of Scheme XI, thiophenol XVIIIA is
initially reacted with cyclic sulfate XL. This

SRL 6071
(C-3021/2)

352

reaction preferably is conducted in an aprotic solvent such as methoxyethyl ether. While the reaction conditions such as temperature and time are not narrowly critical, the reaction preferably is allowed to proceed at about room temperature for about two hours. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield can be improved by using about 1.01 to 1.3 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIIA present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIIA present.

In the process of the invention, thiophenol XVIIIIA also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing thiophenol XVIIIIA prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the hydrogen atom from the mercaptan group attached to the benzene ring of thiophenol XVIIIIA. The resulting sulfur anion of the thiophenol then reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the thiophenol then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group.

The abstracting agent generally is a base having a pH greater than about 10. Preferably, the base is an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; more preferably, the base is sodium hydride. A slight excess of abstracting agent is preferred relative to thiophenol XVIIIIA.

SRL 6071
(C-3021/2)

353

Reaction time and yield is improved by using about 1.0 to about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIa present. More preferably, this ratio is about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIa present.

The sulfate group of the intermediate product of the reaction of thiophenol XVIIIa with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield alcohol XLI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid.

The several reactions involving thiophenol XVIIIa, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need for isolation of any of the intermediates produced.

Alcohol XLI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to aldehyde XLII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

Aldehyde XLII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde XLIII. Preferably, the oxidizing agent is metachloroperbenzoic acid.

Sulfone-aldehyde XLIII likewise is isolated by conventional methods and then cyclized to form the stereoisomeric benzothiepines XLIVa and XLIVb. The cyclizing agent preferably is a base having a pH between about 8 and about 9. More preferably, the base is an alkoxide base, and still more preferably, the

SRL 6071
(C-3021/2)

354

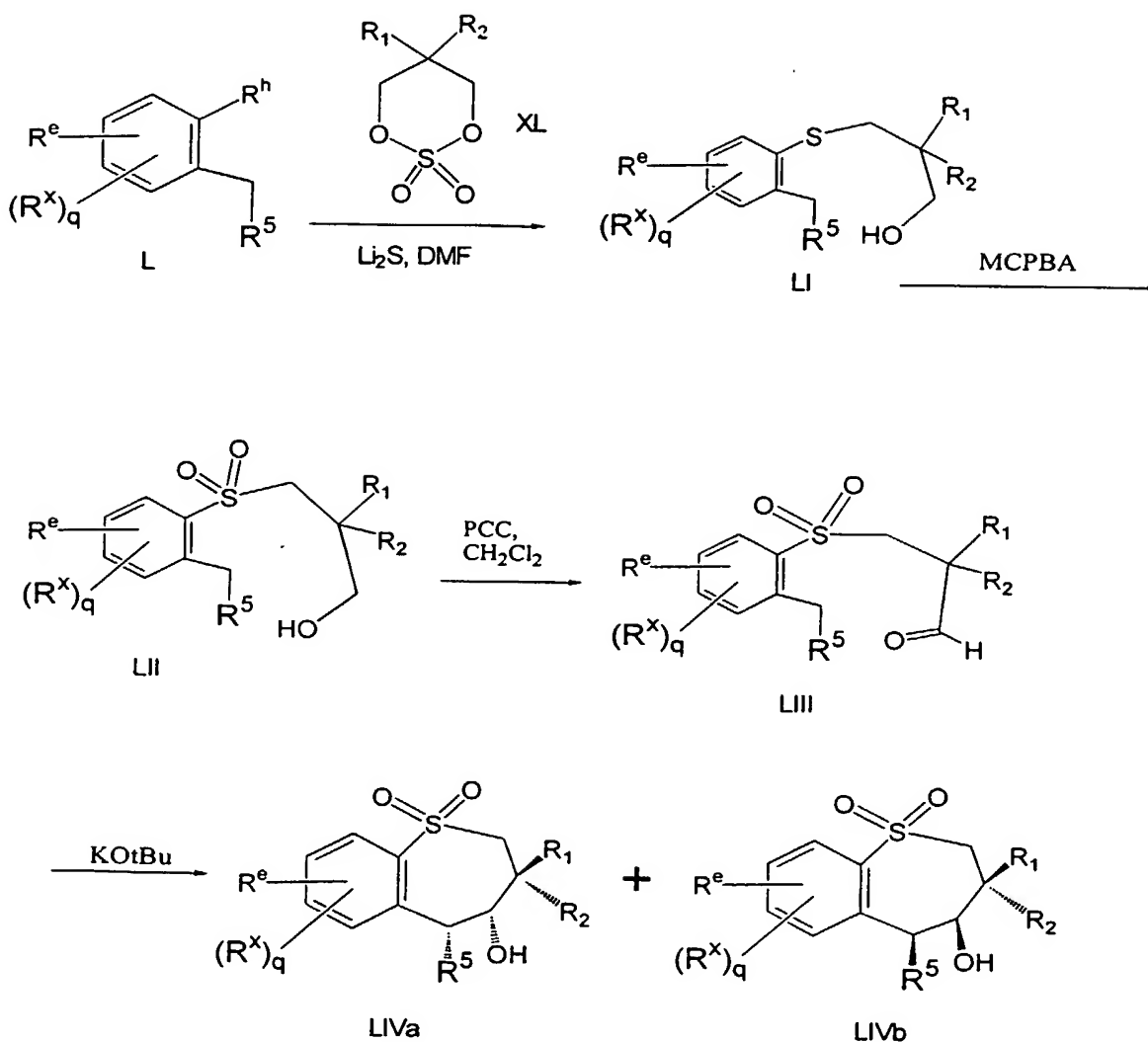
base is potassium tert-butoxide.

5 The two oxidation steps of Scheme XI can be
reversed without adversely affecting the overall
reaction. Alcohol XLI can be oxidized first to yield a
sulfone-alcohol which is then oxidized to yield a
sulfone-aldehyde.

SRL 6071
(C-3021/2)

355

Scheme XII



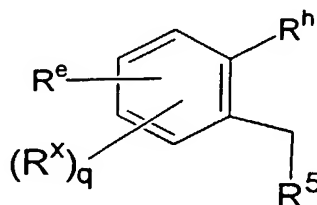
5 Scheme XII illustrates still another route to
 benzothiepine-1,1-dioxides, particularly 3,3-dialkyl
 analogs, starting from the halobenzene **L**. Halobenzene
L can be reacted with cyclic sulfate **XL** disclosed above
 to give the alcohol **LI** which can be oxidized to yield
 10 the sulfone-alcohol **LII**. Sulfone-alcohol **LII** itself
 can be further oxidized to give the sulfone-aldehyde
LIII which can be cyclized to give a stereoisomeric

SRL 6071
(C-3021/2)

356

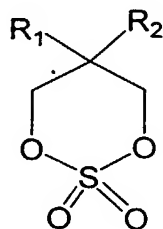
mixture of benzothiepine LIVA and LIVb.

Halobenzene L (which is commercially available or can be synthesized from commercially available halobenzenes by one skilled in the art) has the following formula:



L

wherein R^5 , R^x , and q are as previously defined for the compounds of formula I; R^h is a halogen such as chloro, bromo, fluoro or iodo; and R^e is an electron withdrawing group at the ortho or para position of the halobenzene, and is preferably a p-nitro or o-nitro group. Cyclic sulfate XL can be prepared as set forth in Scheme XI and can have the following formula:



XL

wherein R^1 and R^2 are as previously defined for the compounds of formula I. Preferably, R^1 and R^2 are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^1 and R^2 are n-butyl.

In the process of Scheme XII, halobenzene L is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as dimethyl formamide or N:N-dimethylacetamide,

SRL 6071
(C-3021/2)

357

and more preferably, in dimethyl formamide. Although the reaction conditions such as temperature and time are not narrowly critical, the reaction preferably is allowed to proceed at between about 70°C and about 90°C for about 8 to 12 hours. More preferably, the reaction temperature is maintained at about 80°C. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield is improved by using about 1.1 to 1.3 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present.

In the process of the invention, halobenzene L also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing halobenzene L prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the halogen atom attached to the benzene ring of halobenzene L and replaces that atom with a divalent sulfur atom. The resulting sulfur anion reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the halobenzene then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group. The abstracting agent generally is a dialkali metal sulfide, and preferably it is dilithium sulfide. A slight excess of the abstracting agent is preferred relative to halobenzene L. Reaction time and yield is improved by using about 1.01 to 1.3 equivalents of abstracting agent for each equivalent of halobenzene L present. More preferably,

SRL 6071
(C-3021/2)

358

this ratio is about 1.05 equivalents of abstracting agent for each equivalent of halobenzene L present.

5 The sulfate group of the product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield a mixture of an ester and alcohol LI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid. The ester is then converted to alcohol LI by treatment with an alkali metal hydroxide, 10 preferably sodium hydroxide.

The several reactions involving halobenzene L, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need to isolate any of the intermediates produced.

15 Alcohol LI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to sulfone-alcohol LII. Preferably, the oxidizing agent is metachloroperbenzoic acid. The reaction is conducted in a suitable organic solvent 20 such as methylene chloride or chloroform.

Sulfone-alcohol LII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde LIII. 25 Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.

30 Sulfone-aldehyde XLIII is then converted to the desired benzothiepine-1,1-dioxides according to the procedure previously set forth in Scheme XI.

The two oxidation steps can be reversed without adversely affecting the overall reaction. Alcohol XLI 35 can be oxidized first to yield an aldehyde which is

SRL 6071
(C-3021/2)

359

then oxidized to yield a sulfone-aldehyde.

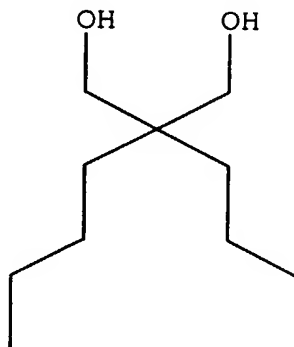
5 Use of the cyclic sulfate reagent instead of a
mesylate reagent in Schemes XI and XII improves the
overall yield and avoids many of the purification
difficulties encountered relative to those reaction
schemes proceeding through a mesylate intermediate.
Overall yields are significantly improved when a cyclic
sulfate is used instead of a mesylate reagent. In
addition, chromatographic separation of the
10 intermediate product of the cyclic sulfate coupling
step of the reaction is not necessary. For example, in
Schemes XI and XII the intermediate is a water soluble
alkali metal salt and the impurities can be removed by
extraction with ether. The intermediate is then
15 hydrolyzed to the desired alcohol.

SRL 6071
(C-3021/2)

360

Example Corresponding to Scheme XI:

Step 1: Preparation of 2,2-dibutyl-1,3-propanediol:



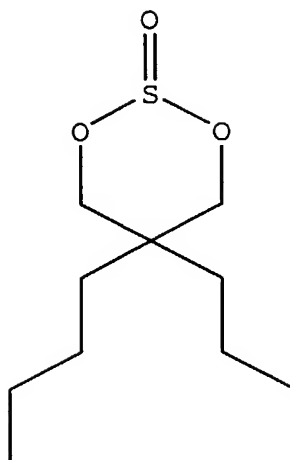
5

Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyl-diethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while
10 maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml
15 of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated under vacuum to give 98.4 g (yield 95%) of the diol as an oil. Proton NMR, carbon NMR and MS confirmed the
20 product.

Step 2: Dibutyl-cyclic-sulfite:

SRL 6071
(C-3021/2)

361

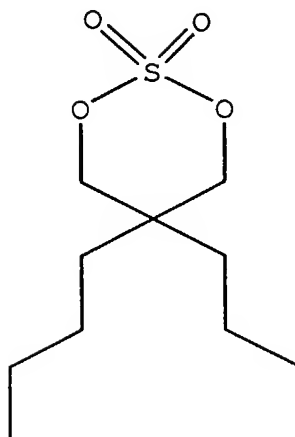


A solution of the dibutyl-diol of step 1 (103 g, 0.5478 mol) in anhydrous methylene chloride (500 ml) and triethylamine (221 g, 4 equivalents, 2.19 mol) was stirred at 0°C under nitrogen. Thionyl chloride (97.78 g, 0.82 mol) was added dropwise to the mixture. Within 5 minutes the solution turned to yellow and then to black when the addition was completed within about half an hour. The reaction was completed within 3 hours (gas chromatography confirmed no starting material was left). The mixture was washed with ice water twice, and brine twice. The organic phase was dried over magnesium sulphate and concentrated under vacuum to give 128 g (yield 100%) of the dibutyl-cyclic-sulfite as a black oil. NMR and MS were consistent with the product.

Step 3: Dibutyl-cyclic sulfate:

SRL 6071
(C-3021/2)

362

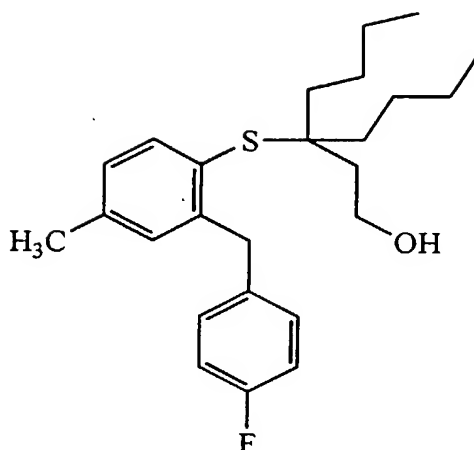


To a solution of the dibutyl-cyclic-sulfite of
step 2 (127.5 g, 0.54 mol) in 600 ml acetonitrile and
500 ml of water cooled in an ice bath under nitrogen
5 was added ruthenium(III) chloride (1 g) and sodium
periodate (233 g, 1.08 mol). The reaction was stirred
overnight and the color of the solution turned black.
Gas chromatography confirmed there was no starting
material left. The mixture was extracted once with 300
10 ml of ether and three times with brine. The organic
phase was dried over magnesium sulphate and passed
through celite. The filtrate was concentrated under
vacuum and gave 133 g (yield 97.8%) of the dibutyl-
cyclic-sulfate as an oil. Proton NMR, carbon NMR and
15 MS confirmed the product.

Step 4: 2-[(2-4'-fluorobenzyl-4-methylphenylthio)
methyl]-2-butylhexanol:

SRL 6071
(C-3021/2)

363



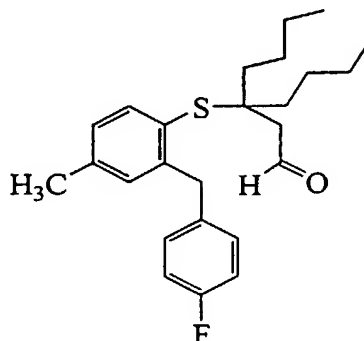
A 60% oil dispersion of sodium hydride (0.27 g, 6.68 mmole) was washed with hexane. The hexane was decanted and 20 ml of methoxyethyl ether was added to the washed sodium hydride and cooled in an ice bath. A mixture of diphenylmethane thiophenol (1.55 g, 6.68 mmole) in 10 ml of methoxyethyl ether was added dropwise over a period of 15 minutes. A mixture of the dibutyl-cyclic-sulfate of step 3 (2.17 g, 8.66 mmole) in 10 ml of methoxyethyl ether was then added. The resulting mixture was stirred for 30 minutes at 0°C and 1 hour at room temperature under nitrogen. Gas chromatography confirmed there was no thiol left. The solvent was evaporated and washed with water and ether two times. The water layer was separated and 20 ml of 10% NaOH was added. This aqueous mixture was boiled for 30 minutes, cooled, acidified with 6N HCl, and boiled for 10 minutes. The mixture was cooled and extracted with ether. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum to give 2.47 g (yield 92.5%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

25

SRL 6071
(C-3021/2)

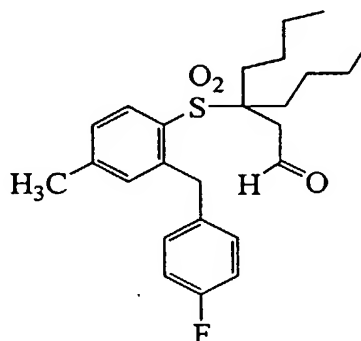
364

Step 5: 2-[(2-4'-fluorobenzyl-4-methylphenylthio)methyl]-2-butylhexanal:



To a solution of the hexanol of step 4 (2 g, 4.9 mmole) in 40 ml of methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmole). The reaction mixture was stirred for 3 hours and filtered through silica gel. The filtrate was concentrated under vacuum to give 1.39 g (yield 70%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 6: 2-[(2-4'-fluorobenzyl-4-methylphenylsulfonyl)methyl]-2-butylhexanal



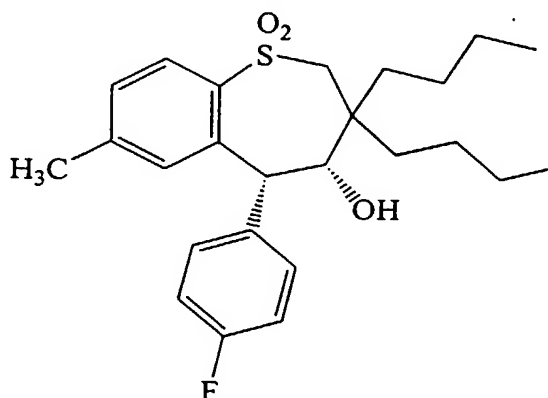
To a solution of the hexanal of step 5 (0.44 g, 1.1 mmole) in 20 ml of methylene chloride cooled by an ice bath under nitrogen was added 70 % metachloroperbenzoic acid (0.54 g, 2.2 mmole). The reaction mixture was stirred for 18 hours and filtered.

SRL 6071
(C-3021/2)

365

The filtrate was washed successively with 10% NaOH(3X), water, and brine, dried over magnesium sulphate, and concentrated under vacuum to give 0.42 g (yield 90%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

Step 7: Cis-3,3-dibutyl-7-methyl-5-(4'-fluoro-phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide:



10

15

20

25

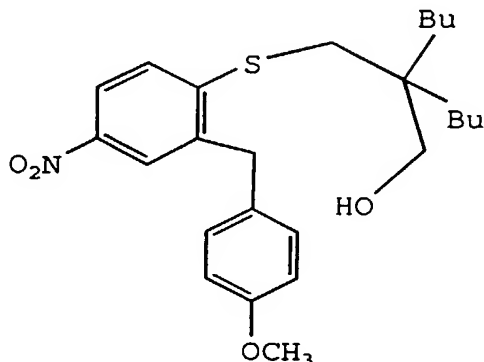
A mixture of the hexanal of step 6 (0.37 g, 0.85 mmole) in 30 ml of anhydrous THF was stirred in an ice bath at a temperature of about 0° C. Potassium-tert-butoxide (102 mg, 0.85 mmole) was then added. After 3 hours thin layer chromatography confirmed the presence of the product and a small amount of the starting material. The crude reaction mixture was acidified with 10% HCl, extracted with ether, washed successively with water and brine, dried with MgSO₄, and concentrated under vacuum. This concentrate was purified by HPLC (10% EtOAc-Hexane). The first fraction came as 0.1 g of the starting material in the form of an oil. The second fraction yielded 0.27 g (75% yield) of the desired benzothiepine as a white solid. Proton NMR, carbon NMR and MS confirmed the product. (M+H=433).

SRL 6071
(C-3021/2)

366

Example Corresponding to Scheme XII

5 Step 1: 2-[(2-4'-methoxybenzyl-4-nitrophenylthio)-
methyl]-2-butylhexanol:



Chlorodiphenylmethane (10g) was dissolved in 25 ml of DMF and lithium sulfide [1.75 g, 1.05 equivalents] was added. The solution color changed to red. The reaction mixture was heated at 80°C overnight. The solution was cooled to 0°C and dibutyl-cyclic-sulfate (9.9g; prepared as set forth in Step 3 of the Scheme XI examples) in 10 ml of DMF was added and stirred at room temperature overnight. The solvent was evaporated and washed successively with water and ether (three times). The water layer was separated and 40 ml of concentrated sulfuric acid was added and the reaction mixture boiled overnight. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum. The product was boiled with 3M of NaOH for 1 hour. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20%

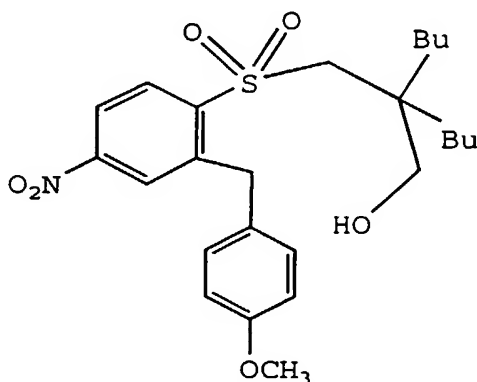
SRL 6071
(C-3021/2)

367

ethyl acetate and hexane, and concentrated under vacuum to give 11.9 g (yield 74%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

5

Step 2: 2-[2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanal:



10 To a solution of the hexanol of step 1 (6 g, 13 mmole) in 50 ml methylene chloride cooled in ice bath under nitrogen was added 70% MCPBA (8.261 g, 33 mmole). The reaction was stirred for 18 hours at room temperature and filtered. The filtrate was washed
15 successively with 10% NaOH (3X), water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under vacuum to
20 give 5 g (yield 77.7%) of the hexanal as a white solid, MP 58-60°C. Proton NMR, C13-NMR and MS confirmed the product.

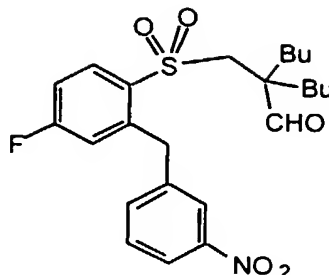
25

Example 1398

SRL 6071
(C-3021/2)

368

Step 1. Preparation of 2

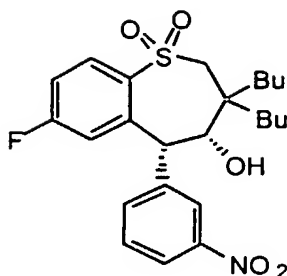


To a solution of 6.0 g of dibutyl 4-fluorobenzene
dialdehyde of Example 1395 (14.3 mmol) in 72 mL of
5 toluene and 54 mL of ethanol was added 4.7 g 3-
nitrobenzeneboronic acid (28.6 mmol), 0.8 g of tetrakis
(triphenylphosphine) palladium(0) (0.7 mmol) and 45 mL
of a 2 M solution of sodium carbonate in water. This
heterogeneous mixture was refluxed for three hours,
10 then cooled to ambient temperature and partitioned
between ethyl acetate and water. The organic layer was
dried over MgSO₄ and concentrated in vacuo.
Purification by silica gel chromatography (Waters Prep-
2000) using ethyl acetate/hexanes (25/75) gave 4.8 g
15 (73%) of the title compound as a yellow solid. ¹H NMR
(CDCl₃) δ 0.88 (t, J = 7.45 Hz, 6H), 0.99-1.38 (m, 8H),
1.62-1.75 (m, 2H), 1.85-2.00 (m, 2H), 3.20 (s, 2H),
4.59 (s, 2H), 6.93 (dd, J = 10.5 and 2.4 Hz, 1H), 7.15
(dt, J = 8.4 and 2.85 Hz, 1H), 7.46-7.59 (m, 2H), 8.05-
20 8.16 (m, 3H), 9.40 (s, 1H).

Step 3. Preparation of 3

SRL 6071
(C-3021/2)

369

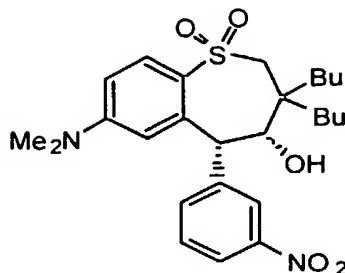


A solution of 4.8 g (10.4 mmol) of **2** in 500 mL THF was cooled to 0 °C in an ice bath. 20 mL of a 1 M solution of potassium t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirring was continued for 30 minutes, then the reaction was quenched with 100 mL of saturated ammonium chloride. The mixture was partitioned between ethyl acetate and water; the organic layer was washed with brine, then dried (MgSO₄) and concentrated in vacuo. Purification by silica gel chromatography through a 100 ml plug using CH₂Cl₂ as eluent yielded 4.3 g (90%) of **3** as a pale yellow foam. ¹H NMR (CDCl₃) δ 0.93 (t, J = 7.25 Hz, 6H), 1.00-1.55 (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 (q_{AB}, J_{AB} = 15.0 Hz, ΔV = 33.2 Hz, 2H), 4.17 (d, J = 6.0 Hz, 1H), 5.67 (s, 1H), 6.34 (dd, J=9.6 and 3.0 Hz, 1H), 7.08 (dt, J = 8.5 and 2.9 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.13 (dd, J = 9.9 and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). MS(FABH⁺) m/e (relative intensity) 464.5 (100), 446.6 (65). HRMS calculated for M+H 464.1907. Found 464.1905.

Step 4. Preparation of **4**

SRL 6071
(C-3021/2)

370

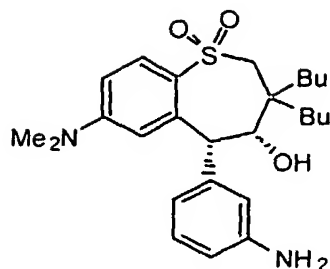


To a cooled (0 °C) solution of 4.3 g (9.3 mmol) of **3** in 30 ml THF contained in a stainless steel reaction vessel was added 8.2 g dimethyl amine (182 mmol). The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-2000) using an ethyl acetate/hexanes gradient (10-40% ethyl acetate) gave 4.0 g (88%) of **4** as a yellow solid. ¹H NMR (CDCl₃) δ 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.0 Hz, DV = 45.6 Hz, 2H), 4.90 (d, J = 9.0 Hz, 1H), 5.65 (s, 1H), 5.75 (d, J = 2.1 Hz, 1H), 6.52 (dd, J = 9.6 and 2.7 Hz, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 8.20 (dd, J = 8.4 and 1.2 Hz, 1H), 8.43 (s, 1H). MS(FABH⁺) m/e (relative intensity) 489.6 (100), 471.5 (25). HRMS calculated for M+H 489.2423. Found 489.2456.

Step 5. Preparation of **5**

SRL 6071
(C-3021/2)

371



To a suspension of 1.0 g (2.1 mmol) of **4** in 100 ml ethanol in a stainless steel Parr reactor was added 1 g
5 10% palladium on carbon. The reaction vessel was sealed, purged twice with H₂, then charged with H₂ (100 psi) and heated to 45 °C for six hours. The reaction vessel was cooled to ambient temperature and the contents filtered to remove the catalyst. The filtrate
10 was concentrated in vacuo to give 0.9 g (96%) of **5**. ¹H NMR (CDCl₃) δ 0.80-0.98 (m, 6H), 1.00-1.52 (m, 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 (s, 2H), 4.14 (s, 1H), 5.43 (s, 1H), 6.09 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, J = 7.8 and 1.8 Hz, 1H), 6.83 (s, 1H), 6.93 (d, J = 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H). MS(FABH⁺) m/e (relative intensity) 459.7 (100). HRMS calculated for M+H 459.2681. Found 459.2670.

20

Step 6. Preparation of **6**

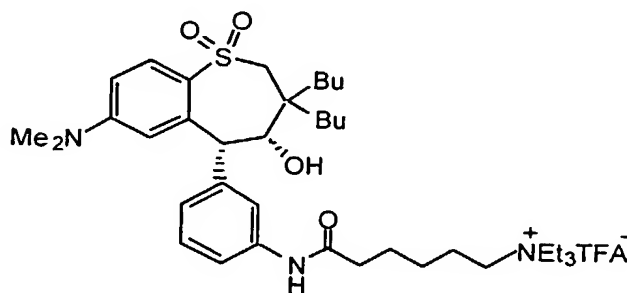
To a solution of 914 mg (2.0 mmol) of **5** in 50 ml THF was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride.
25 Next was added 4 g (39.6 mmol) TEA. The reaction was stirred 10 minutes, then partitioned between ethyl acetate and brine. The organic layer was dried (MgSO₄) and concentrated in vacuo. Purification by silica gel chromatography through a 70 ml MPLC column

SRL 6071
(C-3021/2)

372

using a gradient of ethyl acetate(20-50%) in hexane as eluent yielded 0.9 g (73%) of **6** as a pale yellow oil.
¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.53 (m, 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 4.10 (s, 1H), 5.51 (s, 1H), 5.95 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.3 and 2.7 Hz, 1H), 7.28 (s, 1H), 7.32-7.41 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H).

Step 7. Preparation of **7**



To a solution of 0.9 g (1.45 mmol) of **6** in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55 °C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Purification by reverse-phase silica gel chromatography (Waters Delta Prep 3000) using an acetonitrile /water gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of **7** as a white foam. ¹H NMR (CDCl₃) δ 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (q_{AB}, J_{AB} = 15.6 Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, J =

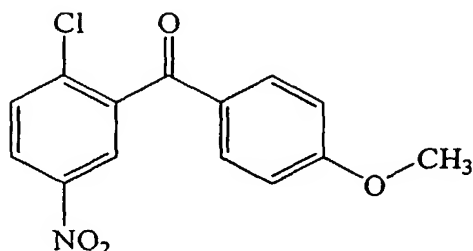
SRL 6071
(C-3021/2)

373

1.8 Hz, 1H), 6.57 (dd, $J = 9.3$ and 2.7 Hz, 1H), 7.24
(t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 8.4$ Hz, 1H), 7.56 (d,
 $J = 8.4$ Hz, 1H), 7.74 (s, 1H), 7.88 (d, $J = 9.0$ Hz,
1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed
5 642.4343.

Example 1398a

10 Step 1



C₁₄H₁₀ClNO₄ fw=291.69

15 In an inert atmosphere, weigh out 68.3 gms
phosphorus pentachloride (0.328mole Aldrich 15,777-5)
into a 2-necked 500ml round bottom flask. Fit flask
with a N₂ inlet adapter and suba seal. Remove from
inert atmosphere and begin N₂ purge. Add 50mls
anhydrous chlorobenzene (Aldrich 28,451-3) to the PCl₅
20 via syringe and begin stirring with magnetic stir bar.

25 Weigh out 60 gms 2-chloro-5-nitrobenzoic acid
(0.298 mole Aldrich 12,511-3). Slowly add to the
chlorobenzene solution while under N₂ purge. Stir at
room temperature overnight. After stirring at room
temperature for ~20hrs, place in oil bath and heat at
50C for 1hr. Remove chlorobenzene by high vacuum. Wash
residue with anhydrous hexane. Dry acid chloride
wt=61.95gms. Store in inert and dry atmosphere.

SRL 6071
(C-3021/2)

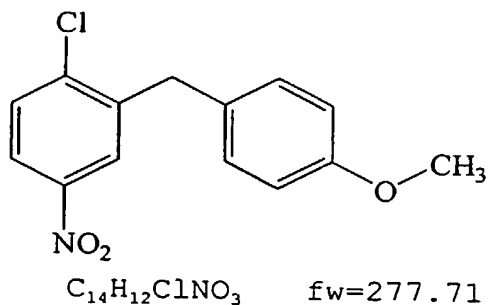
374

In inert atmosphere, dissolve acid chloride with 105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask.

5 Weigh out 45.1gms aluminum chloride (0.34 moles Aldrich 29,471-3) and place in a solid addition funnel. Fit reaction flask with addition funnel and a N₂ inlet adapter. Remove from inert atmosphere. Chill reaction solution with ice bath and begin N₂ purge. Slowly add
10 AlCl₃ to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight .

 Quench reaction by pouring into a solution of 300 mls 1N HCl and ice. Stir 15 min. Extract twice with ether. Combine organic layers and extract twice with
15 2% NaOH, then twice with deionized H₂O. Dry with MgSO₄, filter and rotovap to dryness. Remove anisole by high vacuum. Crystallize product from 90% ethanol 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms. Yield 41%.
20 Obtain NMR and mass spec (m/z=292).

Step 2



25 Dissolve 38.10gms (0.131 moles) of the benzophenone from step 1 in 250mls anhydrous methylene chloride. Place in a 3 liter flask fitted with N₂ inlet, addition funnel and stopper. Stir with magnetic stir bar. Chill solution with ice bath.

SRL 6071
(C-3021/2)

375

5 Prepare a solution of 39.32 gms trifluoromethane sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. Stir 5 minutes after addition is complete.

10 Prepare a solution of 22.85 gms triethyl silane (0.197mole Aldrich 23,019-7) and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. Stir 5 minutes after addition is complete.

15 Prepare a second solution of 39.32 gms trifluoromethane sulfonic acid and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. Stir 5 minutes after addition is complete.

20 Prepare a second solution of 22.85 gms triethyl silane and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N₂. After all additions are made allow to slowly warm to room temperature overnight. Stir under N₂ overnight.

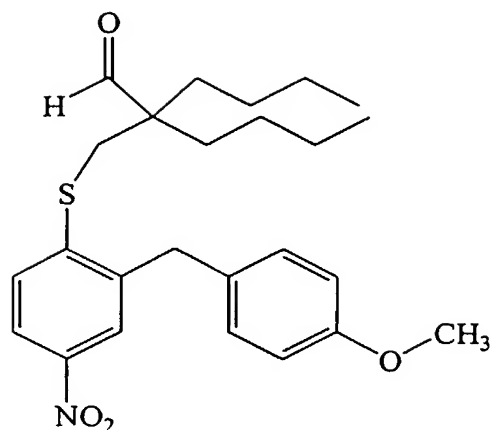
25 Prepare 1300 mls saturated NaHCO₃ in a 4 liter beaker. Chill with ice bath. While stirring vigorously, slowly add reaction mixture. Stir at chilled temperature for 30 min. Pour into a separatory funnel and allow separation. Remove organic layer and extract aqueous layer 2 times with methylene chloride.

30 Dry organic layers with MgSO₄. Crystallize from ethanol. Dry on vacuum line. Dry wt=28.8gms. Confirm by NMR and mass spec (m/z=278).

Step 3

SRL 6071
(C-3021/2)

376



$C_{25}H_{33}NO_4S$ fw=443.61

5 Dissolve 10.12 gms (0.036 moles) of product 2 with
200 mls anhydrous DMSO. Place in a 500 ml round bottom
flask with magnetic stir bar. Fit flask with water
condenser, N_2 inlet, and stopper. Add 1.84 gms Li_2S
(0.040 moles Aldrich 21,324-1). Place flask in oil
bath and heat at $75^\circ C$ under N_2 overnight then cool to
10 room temperature.

Weigh out 10.59 gms dibutyl mesylate (0.040
moles). Dissolve with anhydrous DMSO and add to
reaction solution. Purge well with N_2 , heat overnight
at $80^\circ C$.

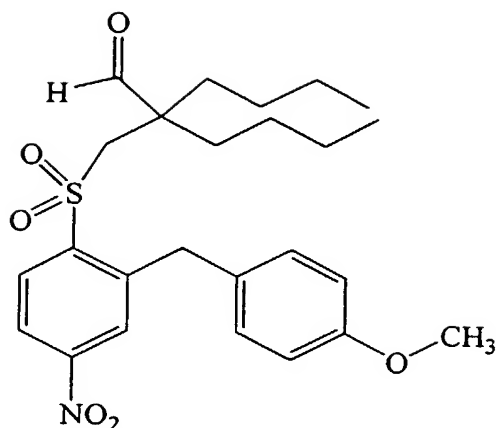
15 Cool to room temperature. Prepare 500 mls of 5%
acetic acid in a 2 liter beaker. While stirring,
slowly add reaction mixture. Stir 30 min. Extract
with ether 3 times. Combine organic layers and extract
with water and sat'd NaCl. Dry organic layer with
20 $MgSO_4$, filter and rotovap to dryness. Dry oil on vacuum
line. Obtain pure product by column chromatography
using 95% hexane and 5% ethyl acetate as the mobile
phase. Dry wt=7.8 gms. Obtain NMR and mass spec
(m/z=444).

25

SRL 6071
(C-3021/2)

377

Step 4



$C_{25}H_{33}NO_6S$ fw=475.61

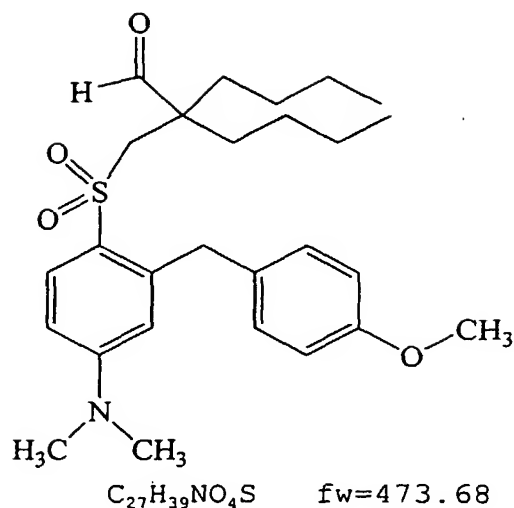
Dissolve 9.33 gms (0.021 moles) of product 3 with 120 mls anhydrous methylene chloride. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice bath under N_2 purge. Slowly add 11.54 gms 3-chloroperbenzoic acid (0.0435 moles, Fluka 25800, ~65%). After addition is complete warm to room temperature and monitor reaction by TLC. Reaction goes quickly to the sulfoxide intermediate but takes 8 hrs to convert to the sulphone. Chill solution over night in freezer. Filter solid from reaction, extract filtrate with 10% K_2CO_3 . Extract aqueous layer twice with methylene chloride. Combine organic layers and dry with $MgSO_4$. Filter and rotovap to dryness. Obtain pure product by crystallizing from ethanol or isolating by column chromatography. Obtain NMR and mass spec ($m/z=476$).

25

SRL 6071
(C-3021/2)

378

Step 5



5 Reaction is done in a 300 ml stainless steel Parr stirred mini reactor. Place 9.68 gms (0.0204 moles) of product 4 in reactor base. Add 160 mls ethanol. For safety reasons next two compounds are added in a N_2 atmosphere glove bag. In glove bag, add 15.3 mls
10 formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich 20,569-9). Seal reactor before removing from glove bag. Purge reactor three times with H_2 . Heat to $55^\circ C$ under H_2 . Run reaction at 200 psig H_2 , $55^\circ C$, and a stir rate of 250 rpm. Run overnight under these conditions.

15 Cool reactor and vent H_2 . Purge with N_2 . Check progress of run by TLC. Reaction is a mixture of desired product and intermediate. Filter reaction mixture over a bed of celite washing well with ether. Rotovap and redissolve with ether. Extract with water.
20 Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line.

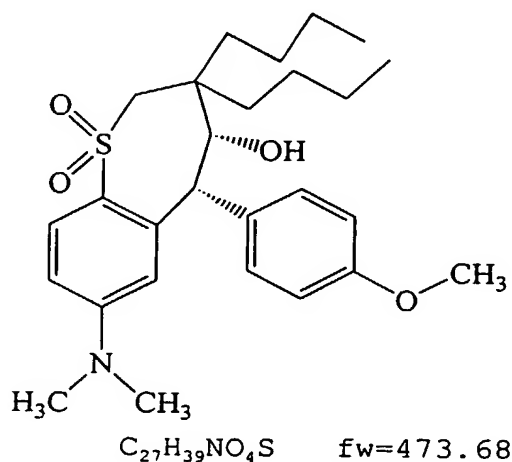
 Charge reactor again with same amounts, seal reactor and run overnight under same conditions.
25 After second run all of the material has been converted

SRL 6071
(C-3021/2)

379

to the desired product. Cool and vent H_2 pressure. Purge with N_2 . Filter over a bed of celite, washing well with ether. Rotovap to dryness. Dissolve with ether and extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line. Obtain NMR and mass spec ($m/z=474$).

Step 6

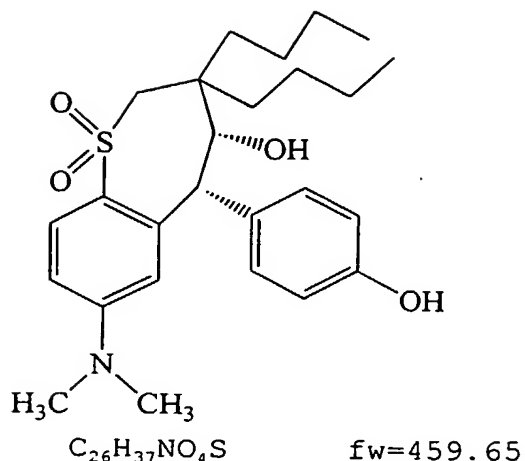


Dissolve 8.97 gms (0.0189 mole) of product 5 with 135 mls anhydrous THF. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice/salt bath under N_2 purge. Slowly add 2.55 gms potassium t-butoxide (0.227 mole Aldrich 15,667-1). After addition is complete, continue to stir at $-10^\circ C$ monitoring by TLC. Once reaction is complete, quench by adding 135 mls 10% HCl stirring 10 min. Extract three times with ether. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Crystallize from ether. Obtain NMR and mass spec ($m/z=474$).

SRL 6071
(C-3021/2)

380

Step 7



5

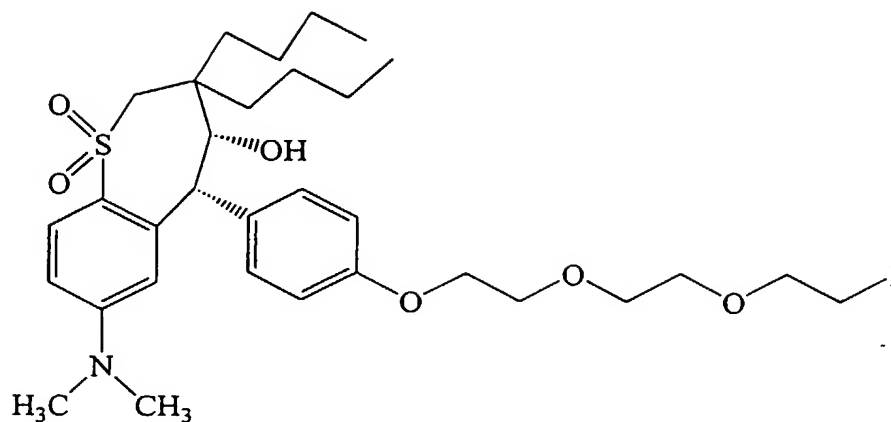
Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N_2 purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

Chill solution with ice bath. Quench with 100 mls 10% K_2CO_3 while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl, once H_2O , and once with saturated NaCl solution. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec ($m/z=460$).

25 Step 8

SRL 6071
(C-3021/2)

381



$\text{C}_{32}\text{H}_{48}\text{NO}_6\text{SI}$ fw=701.71

5 Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0
60% disp. in mineral oil) in a 250 ml round bottom
flask with magnetic stir bar. Fit flask with N_2 inlet
and stopper. Chill NaH with ice bath and begin N_2
purge.

10 Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60
mls anhydrous DMF. Add to the cold NaH. Stir at cold
temperature for 30 min. Add 1.33 gms K_2CO_3 (9.57 mmoles
Fisher P-208).

15 Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane
(43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous
DMF. Add to cold reaction mixture. Warm to room
temperature then heat to 40°C overnight under N_2 .

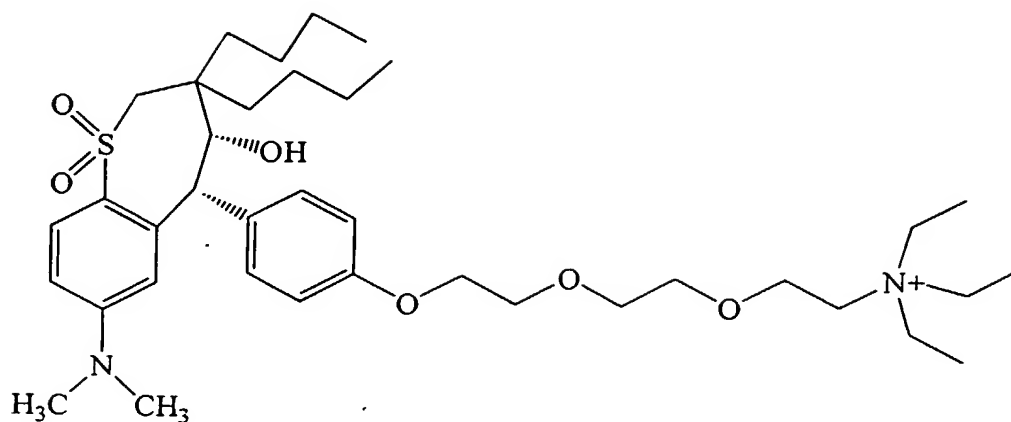
20 Cleanup by diluting with ether and extracting
sequentially with 5% NaOH, H_2O , and saturated NaCl.
Dry organic layer with MgSO_4 , filter and dry. Obtain
pure product by column chromatography using 75% hexane
25% ethyl acetate as the mobile phase. Obtain NMR and
mass spec ($m/z=702$).

25

Step 9

SRL 6071
(C-3021/2)

382



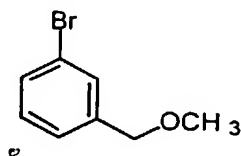
$C_{38}H_{63}N_2O_6SI$ fw=802.90

5 Dissolve 1.0 gms (1.43 mmoles) of product 8 with
10 mls anhydrous acetonitrile. Place in a 3 ounce
Fischer-Porter pressure reaction vessel with magnetic
stir bar. Add 2.9 gms triethyl amine (28.6 mmoles
Aldrich 23,962-3) dissolved in 10 mls anhydrous
10 acetonitrile. Purge well with N_2 then close system .
Heat at $45^\circ C$. Monitor reaction by TLC. Reaction is
usually complete in 48 hrs.

15 Perform cleanup by removing acetonitrile under
vacuum. Redissolve with anhydrous chloroform and
precipitate quaternary ammonium salt with ether.
Repeat several times. Dry to obtain crystalline
product. Obtain NMR and mass spec ($m/z=675$).

20 Example 1399

Step 1. Preparation of '1

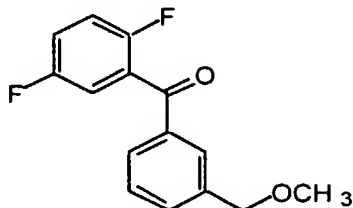


SRL 6071
(C-3021/2)

383

To a solution of 144 g of KOH (2560 mmol) in 1.1 L of DMSO was added 120 g of 2-bromobenzyl alcohol (641 mmol) slowly via addition funnel. Then was added 182 g of methyl iodide (80 mL, 1282 mmol) via addition funnel.
5 Stirred at ambient temperature for fifteen minutes. Poured reaction contents into 1.0 L of water and extracted three times with ethyl acetate. The organic layer was dried over MgSO_4 and concentrated in vacuo. Purified by silica-gel chromatography through a 200 mL
10 plug using hexanes (100%) as elutant yielded 103.2 g (80%) of **1** as a clear colorless liquid. ^1H NMR (CDCl_3) δ 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, 2H), 7.12 (d, $J = 7.45$, 1H), 7.50 (s, 1H).

15 Step 2. Preparation of **2**



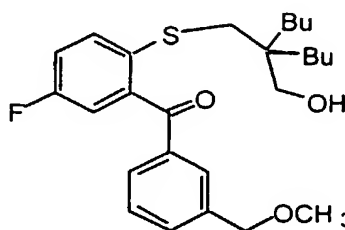
To a cooled ($-78\text{ }^\circ\text{C}$) solution of 95 g (472 mmol) of **1** in 1.5 L THF was added 240 mL of 2.5 M *n*-butyl lithium (576 mmol). The mixture was stirred for one hour, and
20 then to it was added 180 g of zinc iodide (566 mmol) dissolved in 500 mL THF. The mixture was stirred thirty minutes, allowed to warm to $5\text{ }^\circ\text{C}$, cooled to $-10\text{ }^\circ\text{C}$ and to it was added 6 g of $\text{Pd(PPh}_3)_4$ (5.2 mmol) and
25 125 g 2,5-difluorobenzoyl chloride (708 mmol). The mixture was stirred at ambient temperature for 18 hours and then cooled to $10\text{ }^\circ\text{C}$, quenched with water, partitioned between ethyl acetate and water, and washed organic layer with 1N HCL and with 1N NaOH. The
30 organic layer was dried over MgSO_4 and concentrated in vacuo. Purification by silica gel chromatography

SRL 6071
(C-3021/2)

384

(Waters Prep-500) using 5% ethyl acetate/hexanes as elutant gave 53.6 g (43 %) of **2** as an orange oil. ¹H NMR (CDCl₃) d 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, J = 7.50, 1H), 7.57 (d, J = 7.45, 1H), 7.73 (d, J = 7.45, 1H), 7.80 (s, 1H).

Step 3. Preparation of **3**

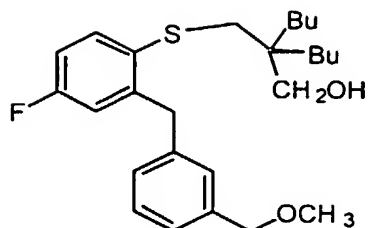


A solution of 53 g (202.3 mmol) of **2** and 11.2 g Li₂S (242.8 mmol) in 250 mL DMF was heated to 100 °C for 18 hours. The reaction was cooled (0 °C) and 60.7 g of X' (the cyclic sulfate compound of example 1397) (242.8 mmol) in 50 mL DMF was added. Stirred at ambient temperature for 18 hours then condensed in vacuo. Added 1 L water to organic residue and extracted twice with diethyl ether. Aqueous layer acidified (pH 1) and refluxed 2 days. Cooled to ambient temperature and extracted with methylene chloride, dried organic layer over MgSO₄ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate / hexanes as elutant gave 42.9 g (48 %) of **3** as a yellow oil. ¹H NMR (CDCl₃) d 0.86 (t, J = 7.25 Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 (s, 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, J = 8.26 Hz and 2.82 Hz, 1H), 7.16 (dt, J = 8.19 Hz and 2.82 Hz, 1H), 7.45 (t, J = 7.65 Hz, 1H), 7.56-7.61 (m, 2H), 7.69 (d, J = 7.85 Hz, 1H), 7.74 (s, 1H).

Step 4. Preparation of **4**

SRL 6071
(C-3021/2)

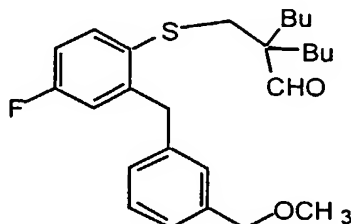
385



To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of **3** in 200 mL of methylene chloride was added 21.6 g trifluoromethane sulfonic acid (12.8 mL, 144 mmol) followed by the addition of 22.4 g triethyl silane (30.7 mL, 192.4 mmol). Stirred at -20 °C for two hours, quenched with water and warmed to ambient temperature.

Partitioned between methylene chloride and water, dried the organic layer over MgSO₄ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate/ hexanes as elutant gave 24.2 g (60%) of **4** as a oil. ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), 1.46 (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (s, 2H), 4.42 (s, 2H), 6.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 7.09 (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 - 7.32 (m, 2H), 7.42 (m, 1H).

Step 5. Preparation of **5**



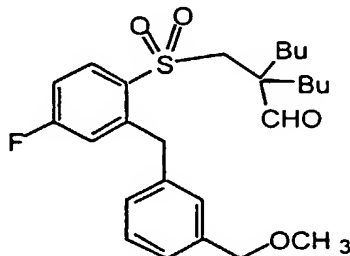
To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of **4** in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water and extracted three times with ethyl acetate. Washed

SRL 6071
(C-3021/2)

386

organics with 5% HCl (300 mL) and then with brine (300 mL), dried organics over MgSO_4 and condensed in vacuo to give 23.1 g (96 %) of **5** as a light brown oil. ^1H NMR (CDCl_3) δ 0.87 (t, $J = 7.05$ Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, $J = 9.66$ Hz and 2.82 Hz, 1H), 6.91 (t, $J = 8.62$ Hz, 1H), 7.07 (d, $J = 7.46$ Hz, 1H), 7.14 (s, 1H), 7.19 (d, $J = 7.65$ Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, $J = 8.66$ Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

Step 6. Preparation of **6**

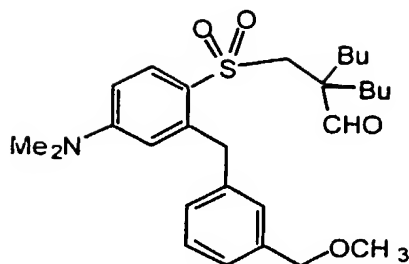


To a cooled (0°C) solution of 23.1 g (53.6 mmol) of **5** in 200 mL methylene chloride was added 28.6 g meta chloroperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na_2SO_3 , partitioned between water and methylene chloride. Dried organic layer over MgSO_4 and condensed in vacuo to give 24.5 g (98%) of **6** as a light yellow oil. ^1H NMR (CDCl_3) δ 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (s, 2H), 3.39 (s, 3H), 4.44 (s, 2H), 4.50 (s, 2H), 6.93 (d, $J = 9.07$ Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (s, 1H), 9.38 (s, 1H).

Step 7. Preparation of **7**

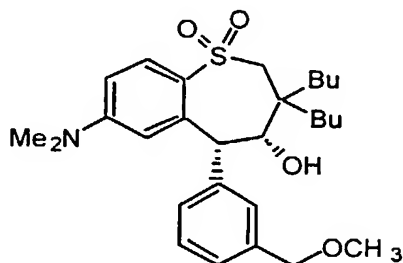
SRL 6071
(C-3021/2)

387



To a solution of 24.5 g (52.9 mmol) of **6** in 20 mL of THF contained in a stainless steel reaction vessel was added 100 mL of a 2.0 M solution of dimethyl amine and 20 mL of neat dimethyl amine. The vessel was sealed and heated to 110 °C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 15 % ethyl acetate/hexanes gave 21.8 g (84 %) of **7** as a clear colorless oil. ¹H NMR (CDCl₃) δ 0.85 (t, J = 7.25 Hz, 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 - 1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, 2H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (s, 1H), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 1H), 9.36 (s, 1H).

Step 8. Preparation of **8**



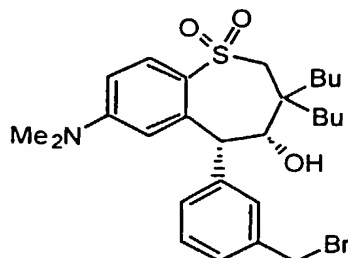
A solution of 21.8 g (44.8 mmol) of **7** in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium

SRL 6071
(C-3021/2)

388

t-butoxide was added slowly, maintaining the temperature at $<5^{\circ}\text{C}$. Stirred for 30 minutes, then quenched with 50 mL of saturated ammonium chloride. The organic layer was partitioned between ethyl acetate and water, dried over MgSO_4 and concentrated in vacuo. Purification by recrystallization from ~10% ethyl acetate/hexanes gave 15.1 g of **8** as a white solid. The mother liquor was purified by silica gel chromatography (Waters Prep-500) using 30% ethyl acetate/hexanes as the elutant to give 3.0 g of **8** as a white solid. MS (FAB Li^+) m/e 494.6. HRMS (EI $^+$) calculated for $\text{M}+\text{H}$ 487.2756. Found 487.2746.

Step 9. Preparation of **9**

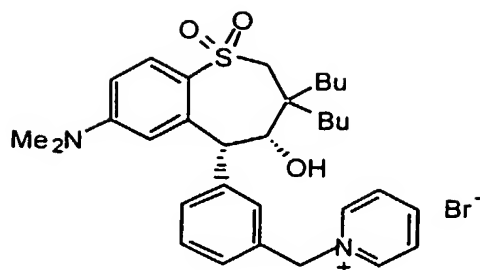


A solution of 2.0 g (4.1 mmol) of **8** in 20 mL of methylene chloride was cooled to -60°C . 4.1 mL of a 1M solution of boron tribromide was added. Stirred at ambient temperature for thirty minutes. Cooled reaction to $\sim 10^{\circ}\text{C}$ and quenched with 50 mL of water. The organic layer was partitioned between methylene chloride and water, dried over MgSO_4 and concentrated in vacuo. Purification by recrystallization from 50% ethyl acetate/methylene chloride gave 1.95 g (89%) of **9** as a white solid. MS (FAB H^+) m/e 537. HRMS (FAB) calculated for M 536.1834. Found 536.1822.

Step 10. Preparation of **10**

SRL 6071
(C-3021/2)

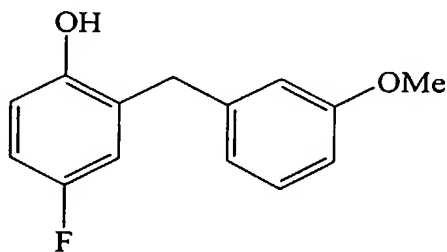
389



A solution of 1.09 g (2.0 mmol) of **9** and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacuo. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of **10** as an off white solid. MS (FAB⁺) m/e 535.5.

Example 1400

Step 1



$C_{14}H_{13}O_2F$ fw=232.25

A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N₂ gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N₂.

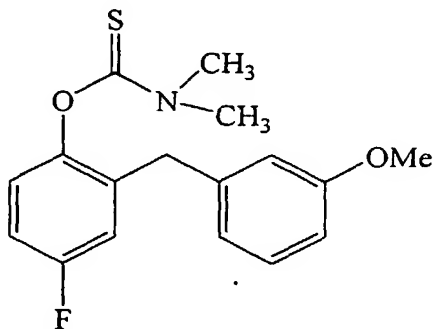
A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl

SRL 6071
(C-3021/2)

390

chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H₂O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aq. KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ¹H NMR and MS [(M + H)⁺ = 233] confirmed desired structure.

Step 2



C₁₇H₁₈NO₂FS fw=319.39

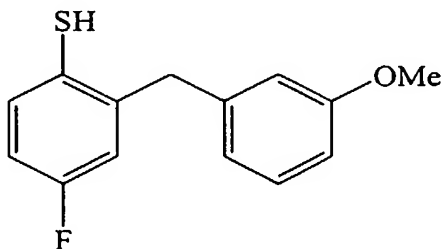
A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N₂ gas adaptor. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenol

SRL 6071
(C-3021/2)

391

(455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride
5 (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H₂O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H₂O and saturated aqueous NaCl, dried (MgSO₄), filtered, and concentrated in vacuo to give
10 the product (605.3g, 97% yield). ¹H NMR and MS [(M+H)⁺ = 320] confirm desired structure.

Step 3



C₁₄H₁₃OFS fw=248.32

A 12-liter, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and reflux condenser. The
20 system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and
25 then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture

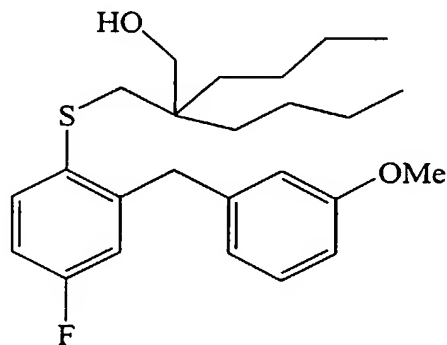
SRL 6071
(C-3021/2)

392

was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H₂O. The aqueous extracts were combined, acidified with concentrated HCl, and extracted with ethyl ether.

The ether extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ¹H NMR confirmed desired structure.

Step 4



C₂₅H₃₅O₂FS fw=418.61

A 5-liter, 3-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-

thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C.

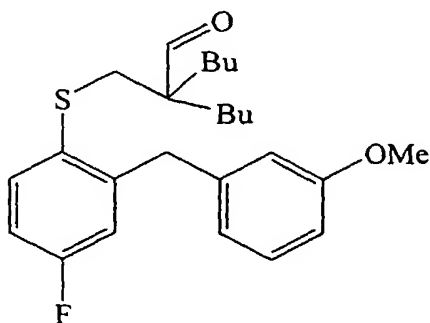
Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature, 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H₂O. The aqueous solution was washed with ethyl ether, and concentrated H₂SO₄ was added. The aqueous solution was heated to reflux for 30 min,

SRL 6071
(C-3021/2)

393

cooled to room temperature, and extracted with ethyl ether. The ether solution was dried (MgSO_4), filtered, and conc'd *in vacuo* to give an amber oil (143.94g/85% yield). ^1H NMR and MS [$(\text{M} + \text{H})^+ = 419$] confirm the
5 desired structure.

Step 5



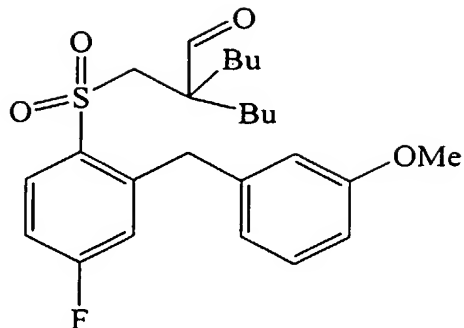
$\text{C}_{25}\text{H}_{33}\text{O}_2\text{FS}$ fw=416.59

A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2 . The corresponding alcohol
15 (143.94g/343.8mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2 . The filtrate was
20 concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ^1H NMR and MS [$(\text{M} + \text{H})^+ = 417$] confirm the desired structure.

SRL 6071
(C-3021/2)

394

Step 6



C₂₅H₃₃O₄FS fw=448.59

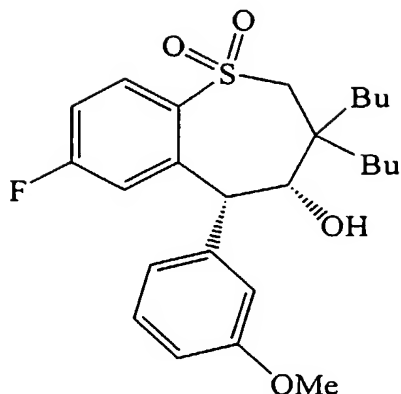
- 5 A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. The corresponding sulfide (110.6g/265.5mmol) and CH₂Cl₂ (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K₂CO₃. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried (MgSO₄), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ¹H NMR confirmed the desired structure.

20

SRL 6071
(C-3021/2)

395

Step 7



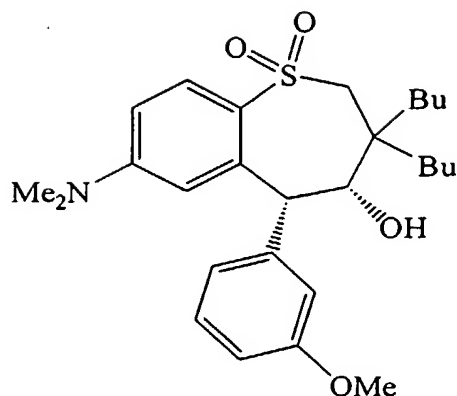
C₂₅H₃₃O₄FS fw=448.59

- 5 A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N₂. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 C.
- 10 3 Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was purified
- 15 by recryst. from 80/20 hexane/ethyl acetate to give a white solid (32.18 g). The mother liquor was concentrated *in vacuo* and recrystelized from 95/5 toluene/ethyl acetate to give a white solid (33.60g/ combined yield: 71%). ¹H NMR confirmed the desired
- 20 product.

SRL 6071
(C-3021/2)

396

Step 8



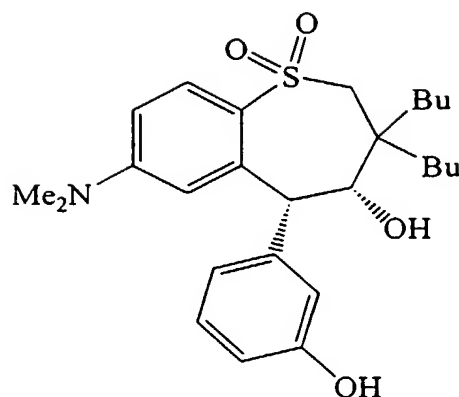
C₂₇H₃₉O₄NS fw=473.67

- 5 A Fisher porter bottle was fitted with N₂ line and magnetic stirrer. The system was purged with N₂. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78 C. Dimethylamine (17.1g/379mmol) was condensed via a
- 10 CO₂/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60 C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H₂O, saturated aqueous
- 15 NaCl, dried (MgSO₄), filtered, and concentrated in vacuo to give a white solid (28.5g/96% yield). ¹H NMR confirmed the desired structure.

SRL 6071
(C-3021/2)

397

Step 9



C₂₆H₃₇O₄NS fw=459.64

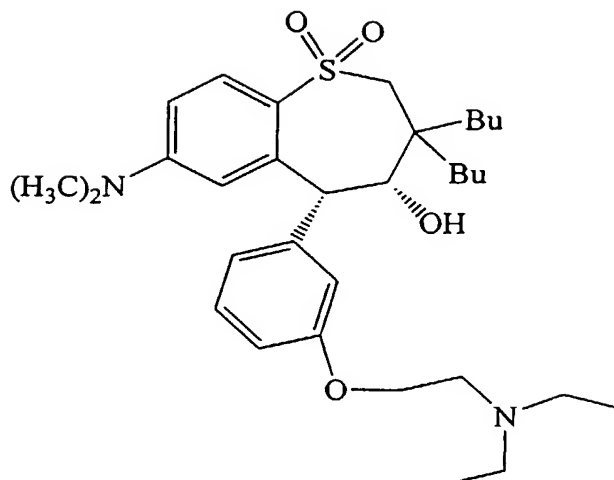
5 A 250-mL, 3-neck, round-bottom flask was equipped with
N₂ gas adaptor and magnetic stirrer. The system was
purged with N₂. The corresponding methoxy-compound
(6.62g/14.0mmol) and CHCl₃ (150 mL) were added. The
reaction mixture was cooled to -78 C, and boron
10 tribromide (10.50g/41.9mmol) was added. The mixture
was allowed to warm to room temperature After 4 h, the
reaction mixture was cooled to 0 C and was quenched
with 10% K₂CO₃ (100 mL). After 10 min, the layers were
separated, and the aqueous layer was extracted two
15 times with ethyl ether. The CHCl₃ and ether extracts
were combined, washed with saturated aqueous NaCl,
dried (MgSO₄), filtered, and concentrated *in vacuo* to
give the product (6.27g/98% yield). ¹H NMR confirmed
the desired structure.

20

SRL 6071
(C-3021/2)

398

Step 10



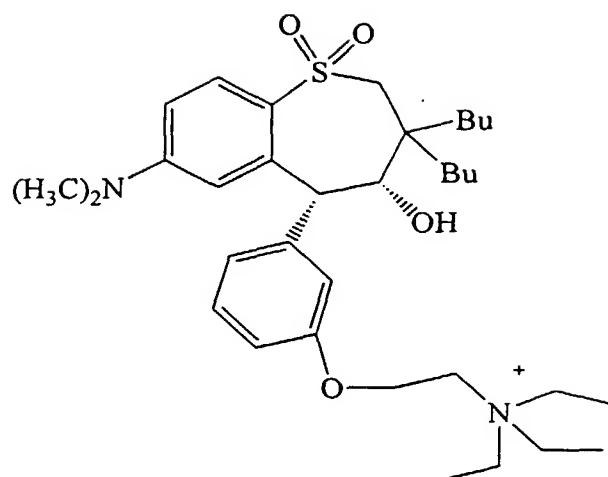
5 In a 250 ml single neck round bottom Flask with stir
bar place 2- diethylaminoethyl chloride hydrochloride
(fw 172.10g/mol) Aldrich D8, 720-1 (2.4 mmol, 4.12g),
34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15
10 minutes and then separate by ether extraction and dry
over anhydrous potassium carbonate.

In a separate 2-necked 250 ml round bottom flask with
stir bar add sodium hydride (60% dispersion in mineral
oil, 100 mg , 2.6 mmol) and 34 ml of DMF. Cool to ice
15 temperature. Next add phenol product(previous step) 1.1
g (2.4 mmol) in 5 ml DMF and the ether solution
prepared above. Heat to 40C for 3 days. The product
which contained no starting material by TLC was diluted
with ether and extracted with 1 portion of 5% NaOH,
20 followed by water and then brine. The ether layer was
dried over magnesium sulfate and isolated by removing
ether by rotary evaporation (1.3 gms). The product may
be further purified by chromatography (SiO₂ 99% ethyl
acetate/1% NH₄OH at 5ml/min.). Isolated yield: 0.78 g
25 (mass spec , and H1 NMR)

SRL 6071
(C-3021/2)

399

Step 11



5

The product from step 10 (0.57gms, 1.02 millimole fw
558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was
placed in 5 ml acetonitrile in a fischer-porter bottle
and heated to 45 C for 3 days. The solution was
evaporated to dryness and redissolved in 5 mls of
chloroform. Next ether was added to the chloroform
solution and the resulting mixture was chilled. The
desired product is isolated as a precipitate 0.7272
gms. Mass spec M-I = 587.9 , H NMR).

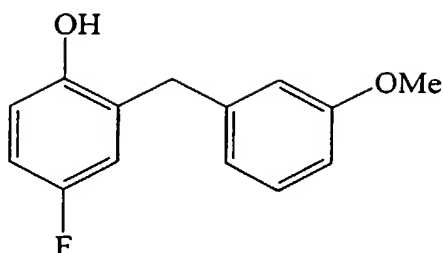
15

SRL 6071
(C-3021/2)

400

Example 1401

Step 1



C₁₄H₁₃O₂F fw=232.25

A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N₂ gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N₂.

A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6 C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H₂O (2.5 L). After 20 min.

stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aqueous KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried over MgSO₄, filtered and

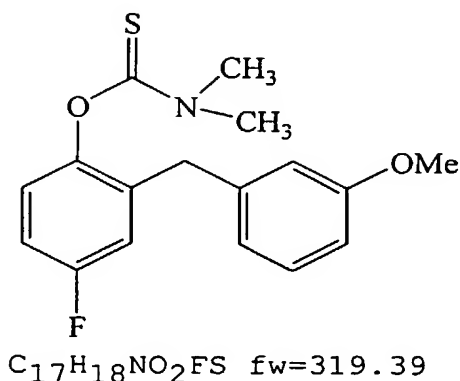
SRL 6071
(C-3021/2)

401

concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg.

^1H NMR and MS $[(M + H)^+ = 233]$ confirmed desired structure.

Step 2

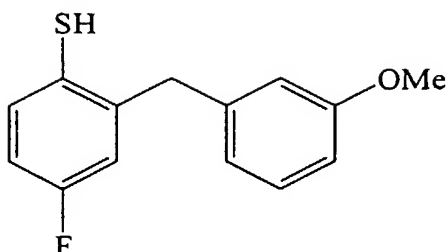


A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N_2 gas adaptor. The system was purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H_2O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl , dried over MgSO_4 , filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ^1H NMR and MS $[(M+H)^+ = 320]$ confirm desired structure.

SRL 6071
(C-3021/2)

402

Step 3



C₁₄H₁₃OFS fw=248.32

5

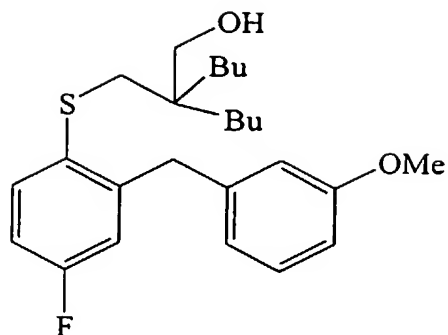
A 12-liter, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H₂O. The aqueous extracts were combined, acidified with conc. HCl, and extracted with ethyl ether. The ether extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ¹H NMR confirmed desired structure.

25

SRL 6071
(C-3021/2)

403

Step 4



$C_{25}H_{35}O_2FS$ fw=418.61

5 A 5-liter, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0 C.

10 Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature. 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H_2O . The aqueous solution was washed with ethyl ether, and conc. H_2SO_4 was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried ($MgSO_4$), filtered, and

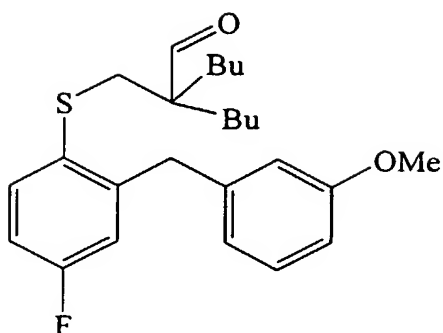
15 concentrated in vacuo to give an amber oil (143.94g/85% yield). 1H NMR and MS [$(M + H)^+ = 419$] confirm the desired structure.

20

25 Step 5

SRL 6071
(C-3021/2)

404

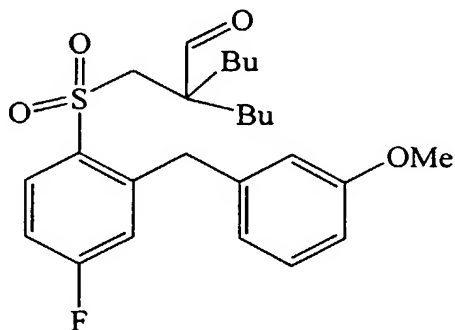


$C_{25}H_{33}O_2FS$ fw=416.59

5 A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, and mechanical stirrer. The system was purged with N_2 . The corresponding alcohol (143.94 g/343.8 mmol) and CH_2Cl_2 (1.0 L) were added and cooled to 0 C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH_2Cl_2 was added. After 20 min, the mixture was filtered through silica gel, washing with CH_2Cl_2 . The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). 1H NMR and MS [$(M + H)^+ = 417$] confirm the desired structure.

15

Step 6



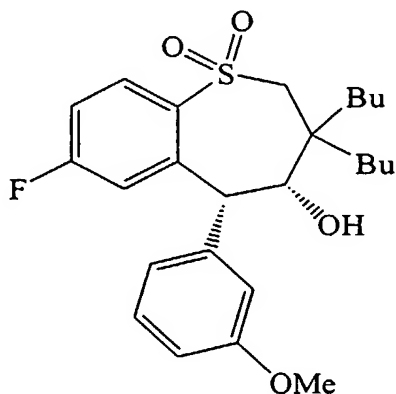
$C_{25}H_{33}O_4FS$ fw=448.59

SRL 6071
(C-3021/2)

405

A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. The corresponding sulfide (110.6g/265.5mmol) and CH₂Cl₂ (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3.5 h, the reaction mixture was cooled to 0 C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K₂CO₃. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried (MgSO₄), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ¹H NMR confirmed the desired structure.

Step 7



C₂₅H₃₃O₄FS fw=448.59

20

A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N₂. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 C.

25

SRL 6071
(C-3021/2)

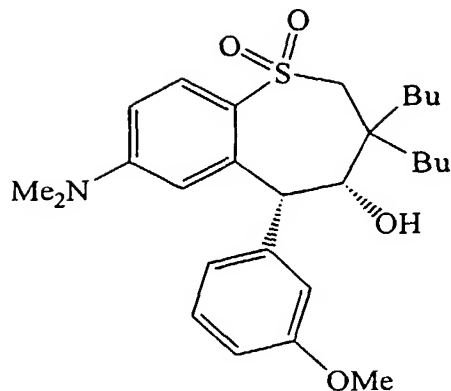
406

Potassium tert-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was purified by recrystallized from 80/20 hexane/ethyl acetate to give a white solid (32.18g). The mother liquor was concentrated *in vacuo* and recrystallized from 95/5 toluene/ethyl acetate to give a white solid (33.60g, combined yield: 71%). ¹H NMR confirmed the desired product.

SRL 6071
(C-3021/2)

407

Step 8



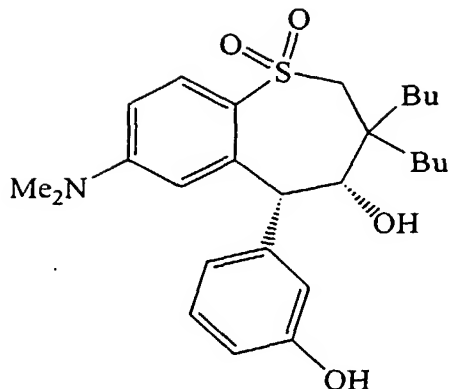
$C_{27}H_{39}O_4NS$ fw=473.67

- 5 A Fisher porter bottle was fitted with N_2 line and magnetic stirrer. The system was purged with N_2 . The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to $-78^\circ C$. Dimethylamine (17.1g/379mmol) was condensed via a
- 10 CO_2 /acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to $60^\circ C$. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H_2O , saturated aqueous
- 15 $NaCl$, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a white solid (28.5g/96% yield). 1H NMR confirmed the desired structure.

SRL 6071
(C-3021/2)

408

Step 9



C₂₆H₃₇O₄NS fw=459.64

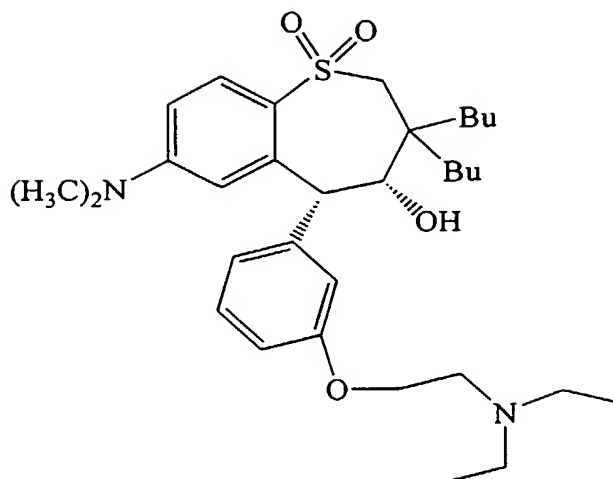
5 A 250-mL, 3-neck, round-bottom flask was equipped
with N₂ gas adaptor and magnetic stirrer. The system
was purged with N₂. The corresponding methoxy-compound
(6.62g/14.0mmol) and CHCl₃ (150 mL) were added. The
reaction mixture was cooled to -78 C, and boron
10 tribromide (10.50g/41.9mmol) was added. The mixture
was allowed to warm to room temperature. After 4 h, the
reaction mixture was cooled to 0 C and was quenched
with 10% K₂CO₃ (100 mL). After 10 min, the layers were
separated, and the aqueous layer was extracted two
15 times with ethyl ether. The CHCl₃ and ether extracts
were combined, washed with saturated aqueous NaCl,
dried over MgSO₄, filtered, and concentrated *in vacuo*
to give the product (6.27g/98% yield). ¹H NMR
confirmed the desired structure.

20

SRL 6071
(C-3021/2)

409

Step 10



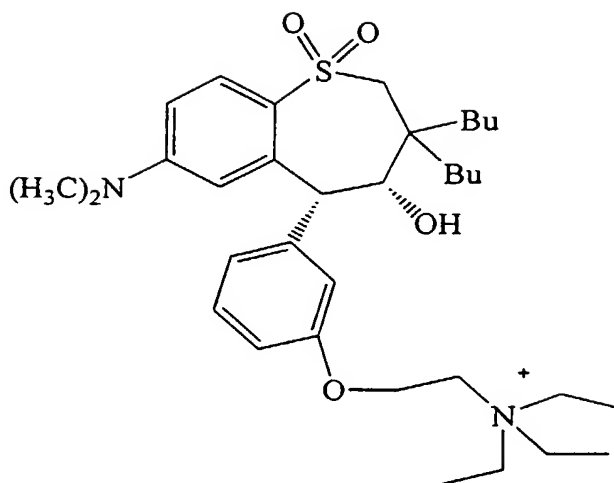
5 In a 250 ml single neck round bottom flask with
stir bar place 2- diethylaminoethyl chloride
hydrochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4
millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N KOH
10 (aqueous). Stir 15 minutes and then separate by ether
extraction and dry over anhydrous potassium carbonate.

15 In a separate 2-necked 250 ml round bottom flask
with stir bar add sodium hydride (60% dispersion in
mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool
to ice temperature. Next add phenol product (previous
step) 1.1 g (2.4 mmol in 5 ml DMF and the ether
solution prepared above. Heat to 40C for 3 days. The
product which contained no starting material by TLC was
diluted with ether and extracted with 1 portion of 5%
20 NaOH, followed by water and then brine. The ether layer
was dried over Magnesium sulfate and isolated by
removing ether by rotary evaporation (1.3 gms). The
product may be further purified by chromatography
(silica 99% ethyl acetate/1% NH4OH at 5ml/min.).
25 Isolated yield: 0.78 g (mass spec , and H1 NMR)

SRL 6071
(C-3021/2)

410

Step 11



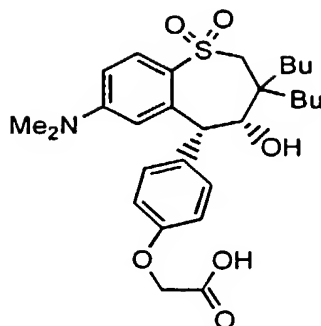
5

The product from step 10 (0.57gms, 1.02 millimole
fw 558.83 g/mole) and iodoethane (1.6 gms (10.02
mmilimoles) was placed in 5 ml acetonitrile in a Fischer-
Porter bottle and heated to 45 C for 3 days. The
10 solution was evaporated to dryness and redissolved in 5
mls of chloroform. Next ether was added to the
chloroform solution and the resulting mixture was
chilled. The desired product is isolated as a
precipitate 0.7272 gms. Mass spec M-I = 587.9, ¹H
15 NMR).

Example 1402

SRL 6071
(C-3021/2)

411



(4R-cis)-5-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
5 benzothiepin-5-yl]phenoxy]pentyl]thio]-1H-tetrazole-1-
acetic acid

Step 1. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol

10 To a stirred solution of 23.66 g of 95% sodium
hydride (0.94 mol) in 600 mL of dry toluene was added
100.0 g of 4-fluorophenol (0.89 mol) at 0°C. The
mixture was stirred at 90°C for 1 hour until gas,
evolution stopped. The mixture was cooled down to room
15 temperature and a solution of 139.71 g of 3-
methoxybenzyl chloride (0.89 mol) in 400 mL of dry
toluene was added. After refluxing for 24 hours, the
mixture was cooled to room temperature and quenched
with 500 mL of water. The organic layer was separated,
20 dried over MgSO_4 , and concentrated under high vacuum.
The remaining starting materials were removed by
distillation. The crude dark red oil was filtered
through a layer of 1 L of silica gel with neat hexane
to yield 53.00 g (25.6%) of the product as a pink
25 solid: ^1H NMR (CDCl_3) δ 3.79 (s, 3H), 3.90 (s, 2H), 4.58
(s, 1H), 6.70-6.74 (m, 1H), 6.79-6.88 (m, 4H), 7.11-
7.16 (m, 2H).

SRL 6071
(C-3021/2)

412

Step 2. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

Step 2a. Preparation of thiocarbamate

To a stirred solution of 50.00 g (215.30 mmol) of
5 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol in 500 mL
of dry DMF was added 11.20 g of 60% sodium hydride
dispersion in mineral oil (279.90 mmol) at 2°C. The
mixture was allowed to warm to room temperature and
26.61 g of dimethylthiocarbamoyl chloride (215.30 mmol)
10 was added. The reaction mixture was stirred at room
temperature overnight. The mixture was quenched with
100 mL of water in an ice bath. The solution was
extracted with 500 mL of diethyl ether. The ether
solution was washed with 500 mL of water and 500 mL of
15 brine. The ether solution was dried over MgSO₄ and
stripped to dryness. The crude product was filtered
through a plug of 500 mL silica gel using 5% ethyl
acetate/hexane to yield 48.00 g (69.8%) of the product
as a pale white solid: ¹H NMR (CDCl₃) δ 3.21 (s, 3H),
20 3.46 (s, 3H), 3.80 (s, 3H), 3.82 (s, 2H), 6.78-6.86 (m,
3H), 6.90-7.00 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 2H).

Step 2b. Rearrangement and hydrolysis of thiocarbamate
to 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

25 A stirred solution of 48.00 g (150.29 mmol) of
thiocarbamate (obtained from Step 2a) in 200 mL of
diphenyl ether was refluxed at 270°C overnight. The
solution was cooled down to room temperature and
filtered through 1 L of silica gel with 2 L of hexane
30 to remove phenyl ether. The rearrangement product was
washed with 5% ethyl acetate/hexane to give 46.00 g
(95.8%) of the product as a pale yellow solid: ¹H NMR
(CDCl₃) δ 3.02 (s, 3H), 3.10 (s, 3H), 3.80 (s, 3H), 4.07
(s, 2H), 6.82-6.86 (m, 3H), 6.93 (dt, *J* = 8.4 Hz, 2.7

SRL 6071
(C-3021/2)

413

Hz, 1H), 7.08 (d, $J = 8.7$ Hz, 2H), 7.49 (dd, $J = 6.0$ Hz, 8.7 Hz, 1H).

To a solution of 46.00 g (144.02 mmol) of the rearrangement product (above) in 200 mL of methanol and 200 mL of THF was added 17.28 g of NaOH (432.06 mmol). The mixture was refluxed under nitrogen overnight. The solvents were evaporated off and 200 mL of water was added. The aqueous solution was washed with 200 mL of diethyl ether twice and placed in an ice bath. The aqueous mixture was acidified to pH 6 with concentrated HCl solution. The solution was extracted with 300 mL of diethyl ether twice. The ether layers were combined, dried over $MgSO_4$ and stripped to dryness to afford 27.00 g (75.5%) of the product as a brown oil: 1H NMR ($CDCl_3$) δ 3.24 (s, 1H), 3.80 (s, 3H), 3.99 (s, 2H), 6.81-6.87 (m, 4H), 7.09 (d, $J = 8.7$ Hz, 2H), 7.27-7.33 (m, 1H).

Step 3. Preparation of dibutyl cyclic sulfate

Step 3a. Preparation of 2,2-dibutyl-1,3-propanediol.

To a stirred solution of di-butyl-diethylmalonate (Aldrich) (150g, 0.55 mol in dry THF (700ml) in an acetone/dry ice bath was added LAH (1 M THF) 662 ml (1.2 eq., 0.66 mol) dropwise maintaining the temperature between -20 to $0^\circ C$. The reaction was stirred at RT overnight. The reaction was cooled to $-20^\circ C$ and 40 ml of water, and 80 mL of 10% NaOH and 80 ml of water were added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated in vacuo to give diol 98.4 g (yield 95%) as an oil. MS spectra and proton and carbon NMR spectra were consistent with the product.

Step 3b. Preparation of dibutyl cyclic sulfite

A solution of 2,2-dibutyl-1,3-propanediol (103 g, 0.548 mol, obtained from Step 3a) and triethylamine

SRL 6071
(C-3021/2)

414

(221 g, 2.19 mol) in anhydrous methylene chloride (500 ml) was stirred at 0°C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise and within 5 min the solution turned yellow and then black when the addition was completed within half an hour. The reaction mixture was stirred for 3 hrs. at 0°C. GC showed that there was no starting material left. The mixture was washed with ice water twice then with brine twice. The organic phase was dried over magnesium sulfate and concentrated under vacuum to give 128 g (100%) of the dibutyl cyclic sulfite as a black oil. Mass spectrum (MS) was consistent with the product.

Step 3c. Oxidation of dibutyl cyclic sulfite to dibutyl cyclic sulfate

To a solution of the dibutyl cyclic sulfite (127.5 g, 0.54 mol, obtained from Step 3b) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium (III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. GC showed that there was no starting material left. The mixture was extracted with 300 ml of ether and the ether extract was washed three times with brine. The organic phase was dried over magnesium sulfate and passed through celite. The filtrate was concentrated under vacuum and to give 133 g (97.8%) of the dibutyl cyclic sulfate as an oil. Proton and carbon NMR and MS were consistent with the product.

Step 4. Preparation of aryl-3-hydroxypropylsulfide

To a stirred solution of 27.00 g (108.73 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)thiophenol (obtained from Step 2) in 270 mL of diglyme was added 4.35 g of 60% sodium hydride dispersion in mineral oil

SRL 6071
(C-3021/2)

415

(108.73 mmol) at 0°C. After gas evolution ceased, 29.94 g (119.60 mmol) of the dibutyl cyclic sulfate (obtained from Step 3c) was added at 0°C and stirred for 10 minutes. The mixture was allowed to warm up to room temperature and stirred overnight. The solvent was evaporated and 200 mL of water was added. The solution was washed with 200 mL of diethyl ether and added 25 mL of concentrated sulfuric acid to make a 2.0 M solution that was refluxed overnight. The solution was extracted with ethyl acetate and the organic solution was dried over MgSO₄ and concentrated in vacuo. The crude aryl-3-hydroxypropylsulfide was purified by silica gel chromatography (Waters Prep 500) using 8% ethyl acetate/hexane to yield 33.00 g (72.5%) of the product as a light brown oil: ¹H NMR (CDCl₃) δ 0.90 (t, J = 7.1 Hz, 6H), 1.14-1.34 (m, 12H), 2.82 (s, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10 (s, 2H), 6.77-6.92 (m, 4H), 7.09 (d, J = 8.7 Hz, 2H), 7.41 (dd, J = 8.7 Hz, 5.7 Hz, 1H).

Step 5. Preparation of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

To a stirred solution of 20.00 g (47.78 mmol) of aryl-3-hydroxypropylsulfide (obtained from Step 4) in 1 L of methylene chloride was added 31.50 g of 96% (1R)-(-)-(8,8-dichloro-10-camphor-sulfonyl)oxaziridine (100.34 mmol, Aldrich) at 2°C. After all the oxaziridine dissolved the mixture was placed into a -30°C freezer for 72 hours. The solvent was evaporated and the crude solid was washed with 1 L of hexane. The white solid was filtered off and the hexane solution was concentrated in vacuo. The crude oil was purified on a silica gel column (Waters Prep 500) using 15% ethyl acetate/hexane to afford 19.00 g (95%) of the enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

SRL 6071
(C-3021/2)

416

as a colorless oil: ^1H NMR (CDCl_3) δ 0.82-0.98 (m, 6H), 1.16-1.32 (m, 12H), 2.29 (d, $J = 13.8$ Hz, 1H), 2.77 (d, $J = 13.5$ Hz, 1H), 3.45 (d, $J = 12.3$ Hz, 1H), 3.69 (d, $J = 12.3$ Hz, 1H), 3.79 (s, 3H), 4.02 (q, $J = 15.6$ Hz, 1H), 6.83-6.93 (m, 3H), 7.00 (d, $J = 8.1$ Hz, 2H), 7.18-7.23 (m, 1H), 7.99-8.04 (m, 1H). Enantiomeric excess was determined by chiral HPLC on a (R,R)-Whelk-O column using 5% ethanol/hexane as the eluent. It showed to be 78% e.e. with the first eluting peak as the major product.

Step 6. Preparation of enantiomerically-enriched aryl-3-propanalsulfoxide

To a stirred solution of 13.27 g of triethylamine (131.16 mmol, Aldrich) in 200 mL dimethyl sulfoxide were added 19.00 g (43.72 mmol) of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide (obtained from Step 5) and 20.96 g of sulfur trioxide-pyridine (131.16 mmol, Aldrich) at room temperature. After the mixture was stirred at room temperature for 48 hours, 500 mL of water was added to the mixture and stirred vigorously.

The mixture was then extracted with 500 mL of ethyl acetate twice. The ethyl acetate layer was separated, dried over MgSO_4 , and concentrated in vacuo. The crude oil was filtered through 500 mL of silica gel using 15% ethyl acetate/hexane to give 17.30 g (91%) of the enantiomerically-enriched aryl-3-propanalsulfoxide as a light orange oil: ^1H NMR (CDCl_3) δ 0.85-0.95 (m, 6H), 1.11-1.17 (m, 4H), 1.21-1.39 (m, 4H), 1.59-1.76 (m, 4H), 1.89-1.99 (m, 1H), 2.57 (d, $J = 14.1$ Hz, 1H), 2.91 (d, $J = 13.8$ Hz, 1H), 3.79 (s, 3H), 3.97 (d, $J = 15.9$ Hz, 1H), 4.12 (d, $J = 15.9$ Hz, 1H), 6.84-6.89 (m, 3H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.19 (dt, $J = 8.4$ Hz, 2.4 Hz, 1H), 8.02 (dd, $J = 8.7$ Hz, 5.7 Hz, 1H), 9.49 (s, 1H).

SRL 6071
(C-3021/2)

417

Step 7. Preparation of the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R)

To a stirred solution of 17.30 g (39.99 mmol) of enantiomerically-enriched aryl-3-propanalsulfoxide (obtained from Step 6) in 300 mL of dry THF at -15°C was added 48 mL of 1.0 M potassium t-butoxide in THF (1.2 equivalents) under nitrogen. The solution was stirred at -15°C for 4 hours. The solution was then quenched with 100 mL of water and neutralized with 4 mL of concentrated HCl solution at 0°C. The THF layer was separated, dried over MgSO₄, and concentrated in vacuo.

The enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R) was purified by silica gel chromatography (Waters Prep 500) using 15% ethyl acetate/hexane to give 13.44 g (77.7%) of the product as a white solid: ¹H NMR (CDCl₃) δ 0.87-0.97 (m, 6H), 1.16-1.32 (m, 4H), 1.34-1.48 (m, 4H), 1.50-1.69 (m, 4H), 1.86-1.96 (m, 1H), 2.88 (d, \underline{J} = 13.0 Hz, 1H), 3.00 (d, \underline{J} = 13.0 Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), 4.48 (s, 1H), 6.52 (dd, \underline{J} = 9.9 Hz, 2.4 Hz, 1H), 6.94 (d, \underline{J} = 9 Hz, 2H), 7.13 (dt, \underline{J} = 8.4 Hz, 2.4 Hz, 1H), 7.38 (d, \underline{J} = 8.7 Hz, 2H), 7.82 (dd, \underline{J} = 8.7 Hz, 5.7 Hz, 1H).

Step 8. Preparation of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a stirred solution of 13.44 g (31.07 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (obtained from Step 7) in 150 mL of methylene chloride was added 9.46 g of 68% *m*-chloroperoxybenzoic acid (37.28 mmol, Sigma) at 0 °C. After stirring at 0 °C for 2 hours, the mixture was allowed to warm up to room temperature and stirred for 4 hours. 50 mL of saturated Na₂SO₃ was added into the mixture and stirred for 30 minutes. The solution was then neutralized with

SRL 6071
(C-3021/2)

418

50 mL of saturated NaHCO_3 solution. The methylene chloride layer was separated, dried over MgSO_4 , and concentrated in vacuo to give 13.00 g (97.5%) of the enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a light yellow solid: ^1H NMR (CDCl_3) δ 0.89-0.95 (m, 6H), 1.09-1.42 (m, 12H), 2.16-2.26 (m, 1H), 3.14 (q, $J = 15.6$ Hz, 1H), 3.87 (s, 3H), 4.18 (s, 1H), 5.48 (s, 1H), 6.54 (dd, $J = 10.2$ Hz, 2.4 Hz, 1H), 6.96-7.07 (m, 3H), 7.40 (d, $J = 8.1$ Hz, 2H), 8.11 (dd, $J = 8.6$ Hz, 5.9 Hz, 1H).

Step 9. Preparation of enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a solution of 13.00 g (28.98 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 8) in 73 mL of dimethylamine (2.0 M in THF, 146 mmol) in a Parr Reactor was added about 20 mL of neat dimethylamine. The mixture was sealed and stirred at 110°C overnight, and cooled to ambient temperature. The excess dimethylamine was evaporated. The crude oil was dissolved in 200 mL of ethyl acetate and washed with 100 mL of water, dried over MgSO_4 , and concentrated in vacuo. Purification on a silica gel column (Waters Prep 500) using 20% ethyl acetate/hexane gave 12.43 g (90.5%) of the enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a colorless solid: ^1H NMR (CDCl_3) δ 0.87-0.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), 2.81 (s, 6H), 2.99 (d, $J = 15.3$ Hz, 1H), 3.15 (d, $J = 15.3$ Hz, 1H), 3.84 (s, 3H), 4.11 (d, $J = 7.5$ Hz, 1H), 5.49 (s, 1H), 5.99 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 8.7$ Hz, 2.4 Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 2H), 7.42 (d,

SRL 6071
(C-3021/2)

419

\underline{J} = 8.4 Hz, 2H), 7.90 (d, \underline{J} = 8.7 Hz, 1H). The product was determined to have 78% e.e. by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. Recrystallization of this solid from ethyl acetate/hexane gave 1.70 g of the racemic product. The remaining solution was concentrated and recrystallized to give 9.8 g of colorless solid. Enantiomeric excess of this solid was determined by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. It showed to have 96% e.e with the first eluting peak as the major product.

Step 10: Demethylation of 5-(4'-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

To a solution of 47 g (99 mmol) of enantiomeric-enriched (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 9) in 500 mL of methylene chloride at -10 °C was added dropwise a solution of boron tribromide (297 mL, 1M in methylene chloride, 297 mmol), and the resulting solution was stirred cold (-5 °C to 0 °C) for 1 hour or until the reaction was complete. The reaction was cooled in an acetone-dry ice bath at -10 °C, and slowly quenched with 300 mL of water. The mixture was warmed to 10 °C, and further diluted with 300 mL of saturated sodium bicarbonate solution to neutralize the mixture. The aqueous layer was separated and extracted with 300 mL of methylene chloride, and the combined extracts were washed with 200 mL of water, brine, dried over MgSO_4 , and concentrated in vacuo. The residue was dissolved in 500 mL of ethyl acetate and stirred with 50 mL of glacial acetic acid for 30 minutes at ambient temperature. The mixture was washed twice with 200 mL of water, 200 mL of brine, dried over MgSO_4 , and

SRL 6071
(C-3021/2)

420

concentrated in vacuo to give the crude 4-hydroxyphenyl intermediate. The solid residue was recrystallized from methylene chloride to give 37.5 g (82%) of the desired 5-(4'-hydroxyphenyl)-7-

5 (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide as a white solid: ^1H NMR (CDCl_3) δ 0.84-0.97 (m, 6H), 1.1-1.5 (m, 10H), 1.57-1.72 (m, 1H), 2.14-2.28 (m, 1H), 2.83 (s, 6H), 3.00 (d, $J = 15.3$ Hz, 1H), 3.16 (d, $J = 15.3$ Hz, 1H), 4.11 (s, 2H), 5.48 (s, 1H), 6.02 (d, $J = 2.4$ Hz, 1H), 6.55 (dd, $J = 9, 2.4$ Hz, 1H), 6.88 (d, 8, 7 Hz, 2H), 7.38 (d, $J = 8.7$ Hz, 2H), 7.91 (d, $J = 9$ Hz, 2H).

Alternatively, enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the intermediate just described, can be prepared via non-enantioselective synthesis followed by chiral chromatography separation. Oxidation of aryl-3-hydroxypropylsulfide (obtained from Step 4) with m-chloroperbenzoic acid (under the similar conditions as in Step 8, but with 2.2 equivalent of m-CPBA) gave the racemic sulfone intermediate. The sulfone was carried through the synthetic sequences (under the same conditions as in Step 7 and Step 9) to give the racemic 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide. The two enantiomers were further separated into the desired enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide by appropriate chiral chromatographic purification.

Step 11: Preparation of ester intermediate

To a solution of 1.0 g (2.18 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 10) in 10 mL

SRL 6071
(C-3021/2)

421

dimethylformamide was added 60 mg (2.38 mmol) of 95% sodium hydride and stirred for 15 minutes. To the reaction mixture was added 400 μ L (2.52 mmol) of benzyl 2-bromoacetate and stirred for two hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 1.30g (98%) of the ester intermediate: ^1H NMR (CDCl_3) δ 0.88-0.94 (m, 6H), 1.13-1.46 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.24 (m, 1H), 2.81 (s, 6H), 3.00 (d, J = 15.1 Hz, 1H), 3.16 (t, J = 15.1 Hz, 1H), 4.11 (s, 1H), 5.26 (s, 2H), 5.49 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 7.37 (s, 5H), 7.42 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H).

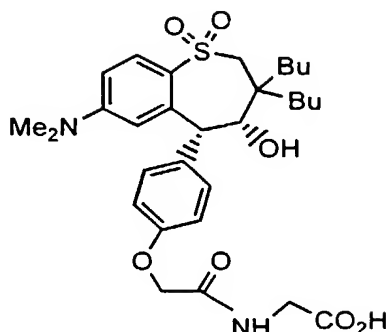
Step 12: Preparation of acid

A solution of 1.30 g (2.14 mmol) of ester intermediate (obtained from Step 1) in 40 mL ethanol with 10% palladium on carbon was placed under an atmosphere of hydrogen gas (40 psi) for three hours. The reaction mixture was filtered through celite and the solvent was evaporated to afford the desired title compound as a white solid: mp 119 - 123 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 0.89-0.94 (m, 6H), 1.19-1.43 (m, 10H), 1.61-1.65 (m, 1H), 2.17-2.21 (m, 1H), 2.85 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (t, J = 14.9 Hz, 1H), 4.12 (s, 1H), 4.72 (s, 2H), 5.51 (s, 1H), 6.17 (s, 1H), 6.74 (d, J = 9.1 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for $\text{C}_{28}\text{H}_{40}\text{NO}_6\text{S}$: 518.2576. Found: 518.2599.

Example 1403

SRL 6071
(C-3021/2)

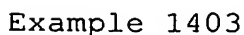
422



(4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

Step 1: Preparation of glycine ester intermediate

To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR (CDCl_3) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 48.9$ Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 7.17 (s, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H).



SRL 6071
(C-3021/2)

424

(4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

5 Step 1: Preparation of glycine ester intermediate

To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR (CDCl_3) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 48.9$ Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 7.17 (s, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H).

Step 2: Preparation of acid

A solution of 7.3 g (12.1 mmol) of glycine ester intermediate (obtained from Step 1) and 1.5 g $\text{LiOH}\cdot\text{H}_2\text{O}$ (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45 °C for 2 hours. This was then cooled to ambient temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 ,

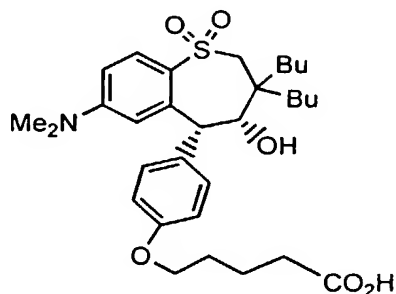
SRL 6071
(C-3021/2)

425

and concentrated in vacuo. Purification by
recrystallization from ethyl acetate gave 5.45 g (78%)
of the desired title compound as a white crystalline
solid: mp 149-150 °C; ¹H NMR (CD₃OD) δ 0.88-0.98 (m,
5 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20
(m, 1H), 2.79 (s, 6H), 3.11 (AB_q, J_{AB} = 15.3 Hz, J =
21.6 Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H),
5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, J = 9.0 Hz, 1H),
7.08 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H),
10 7.76 (d, J = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS(ES+)
Calc'd for C₃₀H₄₂N₂O₇S: 575.2712. Found: 575.2790. Anal.
Calc'd for: C₃₀H₄₂N₂O₇S C, 62.69; H, 7.37; N, 4.87. Found:
C, 62.87; H, 7.56; N, 4.87.

15

Example 1404



20

(4R-cis)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentanoic acid

Step 1: Preparation of ester intermediate

25

A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.0 g, 2.2 mmol, obtained from Example 1402, Step 10) in acetone (10 mL) at 25 °C under N₂ was treated with powdered K₂CO₃ (0.45 g, 3.3 mmol, 1.5 eq.), benzyl 5-

SRL 6071
(C-3021/2)

426

bromovalerate (0.88 g, 3.3 mmol, 1.5 eq.) and a catalytic amount of tetra-*n*-butylammonium iodide (2 mg), and the resulting solution was stirred at 65 °C for 24 hours. The pale amber slurry was cooled to 25 °C and was concentrated in vacuo to provide a yellow residue. Purification by flash chromatography (2.4 x 30 cm silica, 20-40% EtOAc/hexane) afforded the ester intermediate (1.2 g, 86%) as a colorless oil: ¹H NMR (CDCl₃) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.64 (m, 1H), 1.86 (m, 2H), 2.21 (m, 1H), 2.47 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, *J* = 15.1 Hz, *J* = 47.7 Hz, 2H), 4.10 (d, *J* = 7.9 Hz, 1H), 5.13 (s, 2H), 5.47 (s, 1H), 6.00 (d, *J* = 2.5 Hz, 1H), 6.50 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.36 (m, 5H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for C₃₈H₅₁NO₆S: 650.3515. Found: 650.3473.

Step 2: Preparation of acid

A solution of the ester intermediate (0.99 g, 1.5 mmol, obtained from Step 1) in ethanol (7.5 mL) at 25 °C was treated with 5% palladium on carbon (0.15 g, 10 wt %) then stirred under an atmosphere (1 atm) of H₂ via hydrogen balloon. Every 10 min, hydrogen gas was bubbled through the slurry for 1 min, for a total reaction time of 4 hours. The slurry was placed under an atmosphere of N₂ and nitrogen was bubbled through the reaction mixture for 10 min. The mixture was filtered through a plug of Celite® (10 g) and concentrated in vacuo to give a white foam. Purification by flash chromatography (2.6 x 25 cm silica, 1.5% EtOH/CH₂Cl₂) afforded the desired title compound (0.54 g, 63%) as a white foam: mp: 76-79 °C; ¹H NMR (CDCl₃) δ 0.90 (m, 6H), 1.10-1.46 (br m, 10H), 1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, *J*

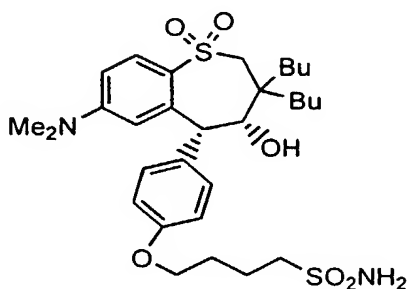
SRL 6071
(C-3021/2)

427

= 15.1 Hz, J = 49.7 Hz, 2H), 4.00 (s, 2H), 4.09 (s, 1H), 5.45 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.39 (m, 5H), 7.39 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.9 Hz, 1H); HRMS. Calc'd for $C_{31}H_{45}NO_6S$: 560.3046. Found: 560.3043.

Example 1405

10



15 (4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy-1-butanesulfonamide

Step 1: Preparation of sulfonic acid intermediate

20 A solution of 7.4 g (16.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in acetone (35 mL) at 25 °C under N_2 was treated with powdered potassium carbonate (3.3 g, 24.1 mmol, 1.5 equiv.) and 1,4-butane sultone (2.5 mL, 24.1 mmol, 1.5 equiv.) and stirred and heated at 65 °C for 64 h.

25 The solution was allowed to cool to 25 °C and quenched by the addition of water (50 mL), until a homogeneous mixture was obtained. The clear and colorless solution was added dropwise to a 4 N HCl solution cooled to 0 °C

SRL 6071
(C-3021/2)

428

over a 30 min period. The mixture was vigorously stirred for 4 h then allowed to warm to ambient temperature and stirred for an additional 16 h. The resultant white precipitate was filtered and washed
5 with water and dried in vacuo to provide 8.8 g (92%) of the desired sulfonic acid as a white solid. A portion of the white solid was recrystallized from CH₃CN/hexane to give the desired sulfonic acid as colorless needles:
10 mp 229-236 °C (decomposed); ¹H NMR (DMSO-d₆) δ 0.82 (m, 6H), 1.02-1.33 (br m, 10H), 1.59 (m, 1H), 1.73 (m, 4H), 2.00 (s, 1H), 2.48 (m, 2H), 2.71 (s, 6H), 2.98 (s, 1H), 3.86 (s, 1H), 3.93 (m, 2H), 5.08 (s, 1H), 5.89 (s, 1H), 6.52 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.9 Hz,
15 1H); Anal. Calc'd for C₃₀H₄₅NO₇S₂: C, 60.48; H, 7.61; N, 2.35. Found: C, 60.53; H, 7.70; N, 2.42.

Step 2: Preparation of 7-(dimethylamino)-benzothiepin-5-yl]phenoxy-1-butanesulfonamide

20 To a solution of 1.12 g (1.88 mmol) of the sulfonic acid (obtained from Step 1) in 10 mL CH₂Cl₂ was added 785 mg (3.77 mmol) PCl₅ and stirred for 1 hour. Water was added and the mixture was extracted and washed with brine. Dried with MgSO₄, filtered and
25 solvent evaporated. To the residue was added 30 mL of 0.5M NH₃ in dioxane and stirred 16 hours. The precipitate was filtered and the solvent evaporated. The residue was purified by MPLC (33% EtOAc in hexane) to afford the desired title compound as a beige solid
30 (125 mg, 11%): mp 108-110 °C; ¹H NMR (CDCl₃) δ 0.85-0.93 (m, 6H), 1.13-1.59 (m, 10H), 1.60-1.67 (m, 1H), 1.94-2.20 (m, 5H), 2.82 (s, 6H), 2.99 (d, *J* = 15.3 Hz, 1H), 3.15 (t, *J* = 15.3 Hz, 1H), 3.23 (t, *J* = 7.7 Hz, 2H), 4.03 (t, *J* = 5.8 Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (s,

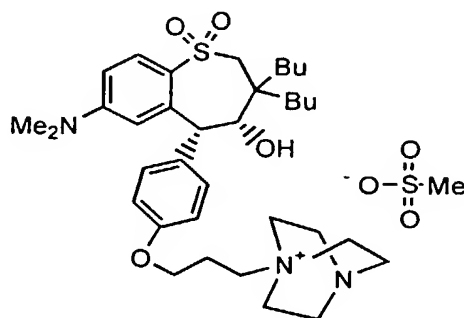
SRL 6071
(C-3021/2)

429

2H), 5.47 (s, 1H), 6.02 (d, $J = 2.4$ Hz, 1H), 6.52 (dd, $J = 8.9, 2.6$ Hz, 1H), 6.91 (d, $J = 8.9$ Hz, 2H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 1H). HRMS. Calc'd for $C_{30}H_{47}N_2O_6S_2$: 595.2876. Found: 595.2874.

5

Example 1406



10

(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-azoniabicyclo[2.2.2]octane, methanesulfonate (salt)

15

Step 1: Preparation of dimesylate intermediate

To a cooled (-20 °C) solution of 5.0 g (65.7 mmol) of 1,3-propanediol in 50 mL of triethylamine and 200 mL of methylene chloride was added 15.8 g (137.9 mmol) of methanesulfonyl chloride. The mixture was stirred for 30 minutes, then warmed to ambient temperature and partitioned between ethyl acetate and 1N HCl. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 13.5 g (89%) of dimesylate intermediate as a clear yellowish oil: 1H NMR ($CDCl_3$) δ 2.12 (quintet, $J = 4.5$ Hz, 4H), 3.58 (s, 6H), 4.38 (t, $J = 5.4$ Hz)

25

SRL 6071
(C-3021/2)

430

Step 2: Preparation of propyl mesylate intermediate

To a solution of 2.4 g (5.2 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 6.0 g (26.1 mmol) of dimesylate intermediate (obtained from Step 1) in 50 mL of acetone was added 3.6 g (26.1 mmol) of K_2CO_3 . The reaction was heated to reflux overnight then cooled to ambient temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 36% ethyl acetate/hexanes afforded 2.8 g (90%) of the propyl mesylate intermediate as a white foam: 1H NMR ($CDCl_3$) δ 0.86-0.95 (m, 6H), 1.06-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.14-2.32 (m, 3H), 2.84 (s, 6H), 3.02 (s, 3H), 3.08 (AB_q, $J_{AB} = 15.0$ Hz, $J = 46.9$ Hz, 4.09-4.18 (m, 3H), 4.48 (t, $J = 6.0$ Hz, 2H), 5.49 (s, 1H), 6.11 (s, 1H), 6.65 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.6$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.94 (d, $J = 8.9$ Hz, 1H).

Step 3: Preparation of quaternary salt

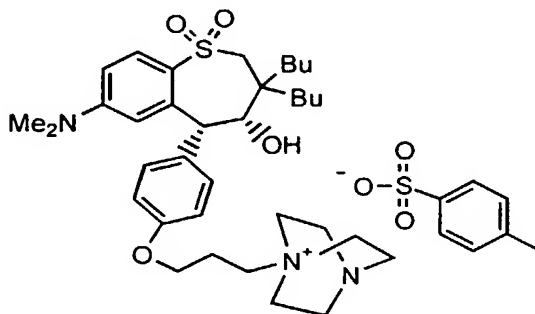
To a solution of 1.2 g (2.0 mmol) of propyl mesylate intermediate (obtained from Step 2) in 20 ml of acetonitrile was added 0.3g (2.9 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction mixture was stirred at 60 °C for three hours, then cooled to ambient temperature and concentrated in vacuo. Purification by trituration with methylene chloride/ethyl ether gave 1.3 g (91%) of the desired title compound as a white solid: mp. (dec) 230-235 °C; 1H NMR ($CDCl_3$) δ 0.86-0.95 (m, 6H), 1.04-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.25 (m, 3H), 2.28-2.39 (m,

SRL 6071
(C-3021/2)

431

2H), 2.83 (s, 6H), 3.04 (s, 3H), 3.09 (AB_q, $J_{AB} = 15.6$ Hz, $J = 42.2$ Hz, 2H) 3.22-3.32 (m, 6H), 3.56-3.66 (m, 6H), 3.73-3.83 (m, 2H), 4.06-4.17 9m, 3H), 5.47 (s, 1H), 5.97 (s, 1H), 6.51 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 1H). MS (ES+) m/e 612.4. HRMS (ES+) Calc'd for C₃₅H₅₄N₃O₄S⁺: 612.3835. Found: 612.3840.

10 Example 1407



(4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-
azoniabicyclo[2.2.2]octane, 4-methylbenzenesulfonate
(salt)

20 Step 1: Preparation of propyl tosylate intermediate

A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N₂ was treated with powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,3-propanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting mixture was stirred at 65 °C for 21 hours. The cream-colored slurry was cooled to 25 °C

SRL 6071
(C-3021/2)

432

and was filtered through a sintered glass funnel. The filtrate was concentrated and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2 x 150 mL) and saturated aqueous NaCl (2 x 150 mL), and was dried (MgSO₄) and concentrated in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 x 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl tosylate intermediate (6.0 g, 80%) as a white foam: ¹H NMR (CDCl₃) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.63 (m, 1H), 2.14 (m, 2H), 2.21 (m, 1H), 2.41 (s, 3H), 2.81 (s, 6H), 3.06 (ABq, J = 15.1 Hz, J = 49.0 Hz, 2H), 4.01 (t, J = 5.3 Hz, 2H), 4.10 (m, 1H), 4.26 (t, J = 5.9 Hz, 2H), 5.29 (s, 1H), 5.48 (s, 1H), 5.98 (s, 1H), 6.51 (dd, J = 8.9, 1.8 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.9 Hz, 1H).

Step 2: Preparation of quaternary salt

A solution of the propyl tosylate intermediate (1.05 g, 1.56 mmol, obtained from Step 1) in acetonitrile (15 mL) at 25 °C under N₂ was treated with diazabicyclo[2.2.2]octane (DABCO, 0.26 g, 2.34 mmol, 1.5 eq.) and stirred at 50 °C for 6 hours, then at 25 °C for 14 hours. The pale amber solution was cooled to 25 °C and concentrated in vacuo to provide an amber oil. The residue was dissolved in a minimal amount of CH₂Cl₂ (5 mL) and diluted with Et₂O (100 mL) while vigorously stirring for 4 hours, during which time a white solid precipitated. The white solid was collected (Et₂O wash) to give the desired title compound (1.11 g, 90%) as a white amorphous solid: mp 136.5-142 °C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.12-1.43 (br m, 9H), 1.61 (m, 1H), 1.65 (m, 1H), 2.18 (m,

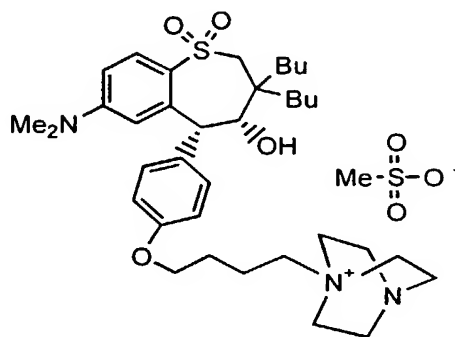
SRL 6071
(C-3021/2)

433

1H), 2.22 (m, 2H), 2.27 (s, 3H), 2.78 (s, 6H), 3.07
(ABq, $J = 15.1$ Hz, $J = 39.5$ Hz, 2H), 3.49 (br s, 6H),
3.68 (m, 1H), 3.74 (br s, 6H), 3.96 (br s, 2H), 4.09
(d, $J = 7.3$ Hz, 1H), 5.46 (s, 1H), 5.96 (d, $J = 2.4$ Hz,
5 1H), 6.49 (dd, $J = 8.9, 2.4$ Hz, 1H), 6.83 (d, $J = 8.5$
Hz, 2H), 7.11 (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.3$ Hz,
2H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.87 (d, $J = 8.9$ Hz,
1H); HRMS. Calc'd for $C_{35}H_{54}N_3O_4S$: 612.3835. Found:
612.3832.

10

Example 1408



15

**(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiopin-5-yl]phenoxy]butyl]-4-aza-1-
azoniabicyclo[2.2.2]octanemethanesulfonate (salt)**

20

Step 1: Preparation of butyl mesylate intermediate

A mixture of 1.00 g (2.18 mmol) of 5-(4'-
hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-
thiopin-1,1-dioxide (obtained from Example 1402, Step
10), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88
25 mmol) of potassium carbonate in 20 mL of acetone was
stirred at reflux overnight. The mixture was
concentrated in vacuo and the crude was dissolved in 30

SRL 6071
(C-3021/2)

434

mL of ethyl acetate. The insoluble solid was filtered off and the filtrate was concentrated in vacuo. The resulting white foam was chromatographed through silica gel column, and eluted with 30% ethyl acetate/hexane to give 1.02 g (77%) of butyl mesylate intermediate as a white solid: ^1H NMR (CDCl_3) δ 0.90 (m, 6H), 1.20-1.67 (m, 12H), 1.98 (m, 4H), 2.22 (m, 1H), 2.83 (s, 6H), 3.04 (s, 3H), 3.08 (ABq, 2H), 4.05 (t, $J = 5.55$ Hz, 2H), 4.11 (d, $J = 6.90$ Hz, 1H), 4.35 (t, $J = 6.0$ Hz, 2H), 5.49 (s, 1H), 6.00 (d, $J = 2.4$ Hz, 1H), 6.52 (dd, $J = 9.0$ Hz, 2.7 Hz, 1H), 6.93 (d, $J = 9.0$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 9.0$ Hz, 1H).

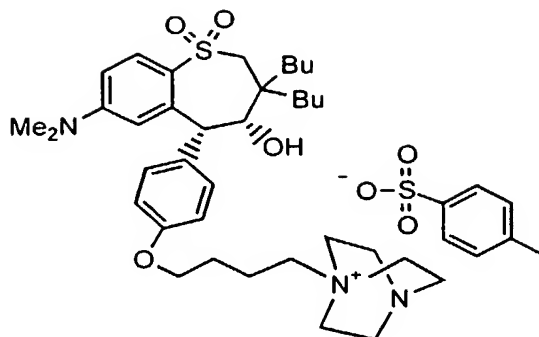
Step 2: Preparation of ester intermediate

A solution of 520 mg (0.85 mmol) of butyl mesylate intermediate (obtained from Step 1) and 191 mg (1.71 mmol) of DABCO in 10 mL of acetonitrile was stirred at 80 °C for 4 hours. The reaction mixture was concentrated in vacuo to yield a white foam. The foam was crushed and washed with ether. The solid was filtered off and dried in vacuo to give 540 mg (88%) of the desired title compound which was recrystallized from methylene chloride and acetone as a white solid: mp 248-251 °C; ^1H NMR (CDCl_3) δ 0.91 (m, 6H), 1.14-1.47 (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H), 2.77 (s, 3H), 2.82 (s, 3H), 3.07 (ABq, 2H), 3.26 (t, $J = 7.1$ Hz, 6H), 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (s, 1H), 5.99 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 8.9$ Hz, 2.6 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 7.89 (d, $J = 9.0$ Hz, 1H).

Example 1409

SRL 6071
(C-3021/2)

435



(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
5 benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-
azoniabicyclo[2.2.2]octane-4-methylbenzenesulfonate
(salt)

Step 1: Preparation of propyl tosylate intermediate

10 A solution of 5-(4'-hydroxyphenyl)-7-(
(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0
g, 10.9 mmol, obtained from Example 1402, Step 10) in
acetone (100 mL) at 25 °C under N₂ was treated with
powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,4-
15 butanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.),
and the resulting solution was stirred at 65 °C for 21
hours. The cream-colored slurry was cooled to 25 °C
and filtered through a sintered glass funnel. The
filtrate was concentrated and the residue was dissolved
20 in EtOAc (150 mL). The organic layer was washed with
saturated aqueous NaHCO₃ (2 x 150 mL) and saturated
aqueous NaCl (2 x 150 mL). The extract was dried
(MgSO₄) and concentrated in vacuo to provide a pale
orange oil. Purification by flash chromatography (4.4
25 x 35 cm silica, 20-30% EtOAc/hexane) afforded the
propyl tosylate intermediate (6.0 g, 80%) as a white
foam: ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.10-1.44 (br m,
10H), 1.61 (m, 1H), 1.84 (m, 4H), 2.19 (m, 1H), 2.43

SRL 6071
(C-3021/2)

436

(s, 3H), 2.80 (s, 6H), 3.03 (ABq, $J = 15.1$ Hz, $J = 46.3$ Hz, 2H), 3.93 (m, 2H), 4.06-4.13 (m, 4H), 5.44 (s, 1H), 5.96 (s, 1H), 6.46 (dd, $J = 8.9$, 1.4 Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.78 (d, $J = 8.9$ Hz, 2H), 7.83 (m, 1H).

Step 2: Preparation of quaternary salt

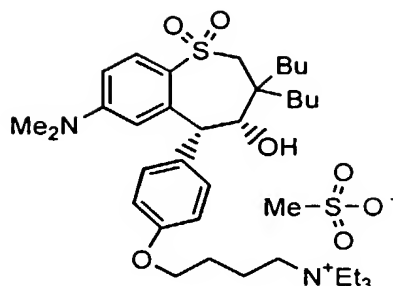
A solution of propyl tosylate intermediate (5.8 g, 8.5 mmol, obtained from Step 1) in acetonitrile (100 mL) at 25 °C under N₂ was treated with diazabicyclo[2.2.2]octane (DABCO, 1.1 g, 10.1 mmol, 1.2 eq.) and stirred at 45 °C for 6 hours. The pale yellow solution was cooled to 25 °C and concentrated in vacuo to provide an off-white solid. The residue was dissolved in a minimal amount of CH₂Cl₂ (5 mL) and diluted with Et₂O (100 mL) while vigorously stirring for 3 hours, during which time a white solid precipitated.

The white solid was collected and recrystallized from EtOAc/hexane to give the desired title compound (5.7 g, 85%) as colorless needles: mp 223-231 °C (decomposed); ¹H NMR (CDCl₃) δ 0.86 (m, 6H), 1.09-1.43 (br m, 12H), 1.61-1.90 (br m, 5H), 2.13 (m, 1H), 2.25 (s, 3H), 2.75 (s, 6H), 3.03 (ABq, $J = 15.1$ Hz, $J = 30.0$ Hz, 2H), 3.05 (br s, 6H), 3.37 (br s, 6H), 3.89 (m, 2H), 4.07 (d, $J = 7.5$ Hz, 1H), 5.39 (s, 2H), 5.97 (d, $J = 1.6$ Hz, 1H), 6.44 (dd, $J = 8.9$, 2.0 Hz, 1H), 6.87 (d, $J = 8.3$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.80 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for C₃₆H₅₆N₃O₄S: 626.3992. Found: 626.3994. Anal. Calc'd for C₄₃H₆₃N₃O₇S₂: C, 64.71; H, 7.96; N, 5.27. Found: C, 64.36; H, 8.10; N, 5.32.

Example 1410

SRL 6071
(C-3021/2)

437



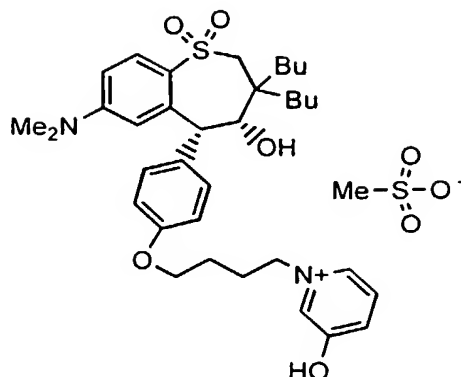
(4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-
tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-
yl]phenoxy]-N,N,N-triethyl-1-butanaminium

A solution of 1 g (1.64 mmol) of the butyl
mesylate intermediate (obtained from Example 1408, Step
1) and 15 mL of triethylamine in 10 mL of acetonitrile
was heated at 50 °C for 2 days. The solvent was
evaporated and the residue was triturated with ether
and ethyl acetate to afford 500 mg (43%) of product as
a semi-solid. ¹H NMR (CDCl₃) δ 0.8 (m, 6 H), 1-1.6 (m,
24 H), 2.1 (m, 1 H), 2.6 (s, 3 H), 2.7 (s, 6 H), 2.9
(d, J = 15 Hz, 1 H), 3.0 (d, J = 15 Hz, 1 H), 3.3 (m,
8 H), 4.0 (m, 4 H), 5.3 (s, 1 H), 5.9 (s, 1 H), 6.4 (m,
1 H), 6.8 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H),
7.8 (d, J = 7 Hz, 1 H). MS m/e 615.

Example 1411

SRL 6071
(C-3021/2)

438



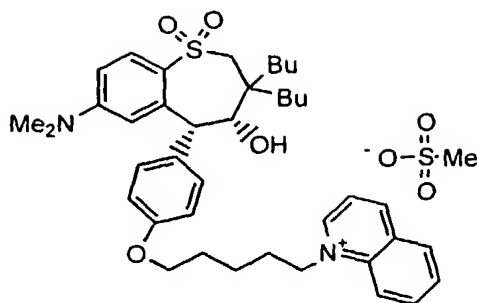
(4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
5 benzothiepin-5-yl]phenoxy]butyl]-3-hydroxypyridinium,
methanesulfonate (salt)

A solution of 1 g (1.64 mmol) of the butyl
mesylate intermediate (obtained from Example 1408, Step
1) and 234 mg (2.46 mmol) of 3-hydroxy pyridine in 1 mL
10 of dimethylformamide was heated at 70 °C for 20 hours.
The solvent was evaporated and the residue was
trituated with ether and ethyl acetate to afford 990
mg (86%) of product as a semi-solid: ¹H NMR (CDCl₃) δ
15 0.9 (m, 6 H), 1-1.5 (m, 10 H), 1.7 (m, 1 H), 1.9 (m, 2
H), 2-2.4 (m, 3 H), 2.9 (s, 6 H), 3.1 (d, J = 15 Hz, 1
H), 3.2 (d, J = 15 Hz, 1 H), 4.1 (m, 3 H), 4.7 (m, 2
H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J
= 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.7 (m, 1 H),
20 8.0 (m, 2 H), 8.2 (m, 1 H), 9.1 (s, 1 H). MS m/e 609.

Example 1412

SRL 6071
(C-3021/2)

439



(4R-cis)-1-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
5 benzothiepin-5-yl]phenoxy]pentyl]quinolinium,
methanesulfonate (salt)

Step 1: Preparation of pentyl mesylate intermediate

To a stirred solution of 231 mg (5.79 mmol, 60%
10 disp.) of NaH in 22 mL of DMF was added 2.05g (4.45
mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-
hydrobenzothiepine-1,1-dioxide (obtained from Example
1402, Step 10), and the resulting solution was stirred
at ambient temperature for 1 hour. To the mixture was
15 added 18.02 g (55.63 mmol) of 1,5-diiodopentane and the
solution was stirred overnight at ambient temperature.
DMF was removed by high vacuum and the residue was
extracted with ethyl acetate and washed with brine.
The extract was dried over MgSO₄, and the concentrated
20 residue was purified by column chromatography to give
the pentyl mesylate intermediate: ¹H NMR (CDCl₃) δ
0.90(q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s,
6h), 3.0 (q, 2H), 3.22 (t, 2H), 3.95 (t, 2H), 4.1 (s,
1H), 5.42 (s, 1H), 6.1 (d, 1H), 6.6 (d, 1H), 6.9 (d,
25 2H), 7.4 (d, 2H), 7.9 (d, 1H).

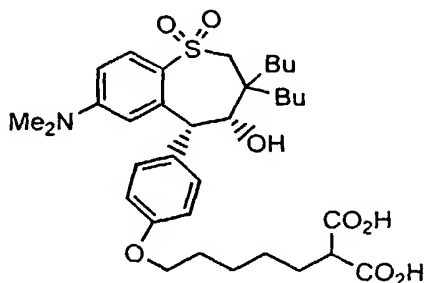
Step 2: Preparation of quaternary salt

SRL 6071
(C-3021/2)

440

To 1.0g (1.53 mmol) of the pentyl mesylate intermediate (obtained from Step 1) was added 3.94 g (30.5 mmol) of quinoline and 30 mL of acetonitrile. The solution was heated at 45 °C under N₂ for 10 days. The concentrated residue was purified by reverse phase C18 column chromatography. The obtained material was exchanged to its mesylate anion by ion exchange chromatography to give the desired title compound as a solid: mp 136 °C; ¹H NMR (CDCl₃) δ 0.95(q, 6H), 1.05-2.25 (m, 18H), 2.8 (s, 9H), 3.0 (q, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.28 (t, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.4 (d, 2H), 7.82 (d, 1H), 7.9 (t, 1H), 8.2 (t, 2H), 8.3 (q, 2H), 8.98 (d, 1H), 10.2 (d, 1H). HRMS. Calc'd for C₄₀H₅₃N₂O₄S: 657.3726. Found: 657.3736. Anal. Calc'd for C₄₀H₅₃N₂O₄S·CH₃O₃S: C, 65.40; H, 7.50; N, 3.72; S, 8.52. Found: C, 62.9; H, 7.42; N, 3.56; S, 8.41.

20 Example 1413



(4S-cis)-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]propanedioic acid

Step 1: Preparation of pentyl bromide intermediate

SRL 6071
(C-3021/2)

441

To a stirred solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was added 6.0 g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and the mixture was stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of dibenzyl ester intermediate

To the mixture of 59 mg (1.476 mmol, 60% disp) of NaH in 27 mL of THF and 9 mL of DMF at 0 °C was added 0.84 g (2.952 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min. To the solution was added 0.5987 g (0.984 mmol) of the pentyl bromide intermediate, and the mixture was stirred at 80 °C overnight. Solvent was removed in vacuo, and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the dibenzyl ester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 1H), 3.9 (t, 2H), 4.1 (d, 1H), 5.18 (s, 4H), 5.42 (s, 1H), 5.95 (s,

SRL 6071
(C-3021/2)

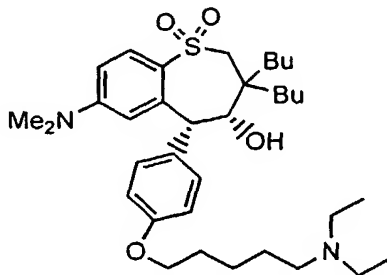
442

1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 12H), 7.85 (d, 1H).

Step 3: Preparation of diacid

5 A suspension of 0.539 g (0.664 mmol) of the dibenzyl ester intermediate (obtained from Step 2) and 25 mg of 10% Pd/C in 30 mL of ethanol was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate
10 was concentrated to give the desired title compound as a solid: mp 118 °C; ¹H NMR (CDCl₃) δ 0.9 (d, 6H), 1.05-2.2 (m, 20H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 1H), 3.95 (s, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.85 (d, 1H).
15 HRMS. Calc'd for C₃₄H₄₉NO₉S: 632.3257. Found: 632.3264. Anal. Calc'd for C₃₄H₄₉NO₈S: C, 64.63; H, 7.82; N, 2.22; S, 5.08. Found: C, 63.82; H, 7.89; N, 2.14; S, 4.93.

20 Example 1414



25 (4R-cis)-3,3-Dibutyl-5-[4-[[5-(diethylamino)pentyl]oxy]phenyl]-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiopin-4-ol 1,1-dioxide

Step 1: Preparation of pentyl iodide intermediate

SRL 6071
(C-3021/2)

443

To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (3 g, 6.53 mmol, obtained from Example 1402, Step 10) in 100 mL of dimethylformamide was added 198 mg (7.83 mmol) of 95% sodium hydride. The mixture was stirred 15 minutes at room temperature and diiodopentane was added. After one hour at room temperature the mixture was diluted in ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with hexane/ethyl acetate (1/5) to afford 2.92g (4.46 mmol) of the pentyl iodide intermediate: ¹H NMR (CDCl₃) δ 0.9 (m, 6 H), 1-1.5 (m, 11 H), 1.6 (m, 3 H), 1.8 (m, 4 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.9 (d, J = 7 Hz, 1 H).

Step 2: Preparation of amine

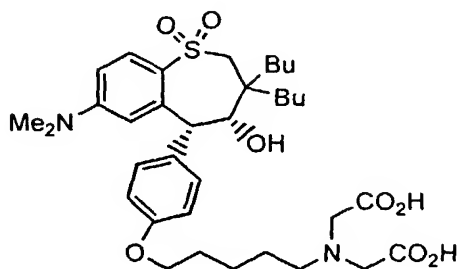
A solution of 550 mg (0.76 mmol) of the pentyl iodide intermediate (obtained from Step 1) and 279 mg (3.81 mmol) of diethylamine in 3 mL of acetonitrile was stirred at 100 °C overnight. The mixture was concentrated in vacuo to yield a yellowish brown foam. The foam was dissolved in 10 mL of ethyl acetate and washed with 50 mL of saturated sodium carbonate solution twice. The ethyl acetate layer was dried over magnesium sulfate and concentrated to yield 390 mg (85%) of the desired title compound as a yellow foamy solid: ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.20-1.47 (m, 12H), 1.53-1.67 (m, 4H), 1.76-1.90 (m, 8H), 2.21 (m,

SRL 6071
(C-3021/2)

444

1H), 2.74-2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, J =
6.3 Hz, 2H), 4.10 (d, J = 7.8 Hz, 1H), 5.48 (s, 1H),
6.00 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.2 Hz, 2.6 Hz,
1H), 6.92 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.4 Hz,
5 2H), 7.90 (d, J = 9.0 Hz, 1H).

Example 1415



(4R-cis)-N-(Carboxymethyl)-N-[5-[4-[3,3-dibutyl-7-
(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-
dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine

Step 1: Preparation of diester intermediate

A mixture of 8.6 g (14.1 mmol) of pentyl bromide
intermediate (obtained from Example 1413, Step 1), 65 g
(0.35 mol) of diethylaminodiacetate and 7.5 g (71
20 mmol) of anhydrous Na_2CO_3 was stirred at 160 °C for 3
hours. The reaction mixture was diluted with water and
extracted with methylene chloride. The volatiles was
removed in vacuo to give 9.6g (95%) of the diester
intermediate. ^1H NMR spectrum was consistent with the
25 structure; MS (M+H) m/e 717.

Step 2: Preparation of diacid

The mixture of the diester intermediate (obtained
from Step 1) and 2.7g (64.3 mmol) of LiOH in THF (75

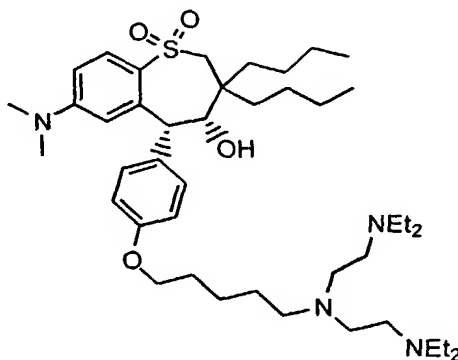
SRL 6071
(C-3021/2)

445

mL) and water (50 mL) was stirred at 40 °C for 18 hours. The reaction mixture was acidified with 1% HCl and extracted with dichloromethane. The residue was triturated with hexane, filtered to give 8.9g (93%) of the desired title compound as a solid: mp 148-162 °C; ¹H NMR (CD₃OD) δ 0.92 (t, 6H), 1.1-1.9 (m, 31H), 2.15 (t, 1H), 2.8 (s, 6H), 3.15 (ABq, 2H), 3.75 (m, 1H), 4.1 (m, 6H), 5.3 (s, 1H), 6.1 (s, 1H), 6.6 (d, 1H), 7.0 (d, 2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M+H) m/e 661. Anal. Calc'd for [C₃₅H₅₂N₂O₈S + 1.5H₂O]: C, 61.11; H, 8.06; N, 4.07; S, 4.66. Found: C, 61.00; H, 7.72; N, 3.89; S, 4.47.

Example 1416

15



(4R-cis)-5-[4-[[5-[bis[2-(diethylamino)ethyl]amino]pentyl]oxy]phenyl]-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) in N,N,N',N'-tetraethyl diethylenetriamine was heated to 80 °C for 4 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO₃. The organic layer was washed with brine, dried over magnesium sulfate, and

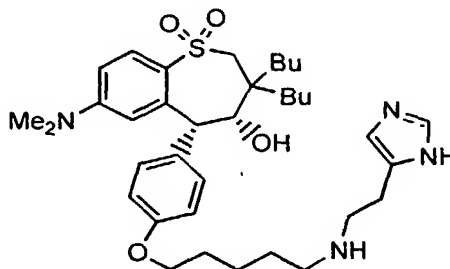
SRL 6071
(C-3021/2)

446

concentrated in vacuo. The residue was purified by reverse phase chromatography. The fractions containing the product were concentrated in vacuo, dissolved in ethyl acetate and washed with saturated NaHCO₃. The residue was dried and concentrated in vacuo to afford 840 mg (74%) of the desired title compound as a thick oil. ¹H NMR (CDCl₃) δ 0.8 (m, 6 H), 1-1.6 (m, 28 H), 1.8 (m, 2 H), 2.1 (m, 1 H), 2.5 (m, 18 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.1 (d, J = 15 Hz, 1 H), 3.9 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.4 (s, 1 H), 6.0 (s, 1 H), 6.4 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS (M+H) *m/e* 743.

15

Example 1417



20

(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-[[2-(1H-imidazol-4-yl)ethyl]amino]pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

25

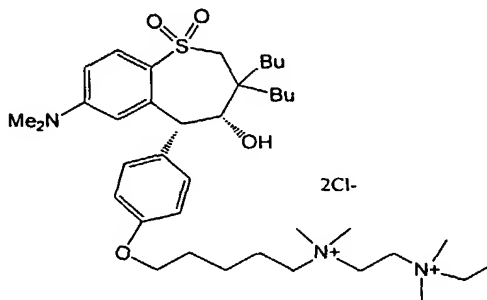
A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) and 3.4 g (30.6 mmol) of histamine was heated to 50 °C for 17 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO₃. The organic layer was washed with

SRL 6071
(C-3021/2)

447

brine, dried over magnesium sulfate, and concentrated
in vacuo. The residue was triturated with ether to
afford 588 mg (60%) of the desired title compound as a
semi-solid: ^1H NMR (CDCl_3) δ 0.9 (m, 6 H), 1-1.7 (m, 14
H), 1.9 (m, 3 H), 2.0 (m, 2 H), 2.2 (m, 1 H), 2.8 (s,
6 H), 3.0 (m, 3 H), 3.2 (m, 2 H), 4.0 (m, 2 H), 4.1 (m,
3 H), 5.5 (s, 1 H), 6.0 (s, 1 H), 6.5 (m, 1 H), 6.8 (s,
1 H), 6.9 (d, $J = 9$ Hz, 2 H), 7.4 (m, 3 H), 7.9 (d, J
 $= 8$ Hz, 1 H). MS (M+H) m/e 639.

Example 1418



**(4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]pentyl]-N'-ethyl-N,N,N',N'-
tetramethyl-1,2-ethanediaminium dichloride**

Step 1: Preparation of pentyl bromide intermediate

A mixture of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.680g, 3.66 mmol, obtained from Example 1402, Step 10) and sodium hydride (0.250g, 6.25 mmol) in 30 mL of DMF was stirred in a dry 100 mL round-bottom flask under N_2 . To this solution was added 1,5-dibromopentane (6.0 mL/44.0 mmol), and the resulting mixture was

SRL 6071
(C-3021/2)

448

5 stirred for 18 hours. The reaction was diluted with
brine (100 mL) and H₂O (20 mL), and the mixture was
extracted with EtOAc (3x50 mL). Organic layers were
combined, dried (MgSO₄), filtered and concentrated in
10 vacuo. Purification by filtration through silica gel
eluting with 20% EtOAc/hexane and evaporation in vacuo
gave pentyl bromide intermediate as a white foamy solid
(1.783g, 80%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H),
1.02-1.56 (m, 10H), 1.58-1.70 (m, 3H), 1.78-2.03 (m,
10 4H), 2.15-2.24 (m, 1H), 2.77 (s, 1H), 2.80 (s, 6H),
3.05 (ABq, 2H), 3.42 (t, 2H), 3.98 (t, 2H), 4.10 (s,
1H), 5.47 (s, 1H), 5.99 (d, 1H), 6.50 (dd, 1H), 6.91
(d, 2H), 7.40 (d, 2H), 7.88 (d, 1H).

15 Step 2: Preparation of mono-quaternary salt

The mixture of pentyl bromide intermediate
(0.853g, 1.40 mmol, obtained from Step 1), N,N,N',N'-
tetramethylethylenediamine (1.0 mL/6.62 mmol) in 30 mL
of acetonitrile was stirred at 40 °C for 12 hours, and
20 the reaction mixture was concentrated in vacuo to give
an off-white foamy solid (1.052g). The crude product
was dissolved in acetonitrile (1.5 mL) and triturated
with ethyl ether. The solvent was decanted to yield a
sticky solid. This trituration method was repeated
25 twice, and the resulting sticky solid was concentrated
in vacuo to give the mono-quaternary salt as an off-
white foamy solid (0.951g, 94%): ¹H NMR (CDCl₃) δ 0.81
(t, 6H), 0.96-1.64 (m, 13H), 1.62-1.85 (m, 4H), 2.03-
2.18 (m, 1H), 2.20 (s, 6H), 2.67 (t, 2H), 2.74 (s, 6H),
30 2.98 (ABq, 2H), 3.30-3.42 (m, 1H), 3.38 (s, 6H), 3.60-
3.75 (m, 4H), 3.90 (t, 2H), 4.01 (s, 1H), 5.37 (s, 1H),
5.92 (s, 1H), 6.41 (dd, 1H), 6.81 (d, 2H), 7.32 (d,
2H), 7.77 (d, 1H).

SRL 6071
(C-3021/2)

449

Step 3: Preparation of di-quaternary salt

The mono-quaternary salt (0.933g, 1.29 mmol, obtained from Step 2), iodoethane (0.300 mL/3.75 mmol), and acetonitrile (30.0 mL) were combined in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N₂, sealed, equipped with magnetic stirrer, and heated to 50 °C. After 24 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give a yellow foamy solid (1.166g). The solid was dissolved in methylene chloride/acetonitrile and precipitated with ethyl ether. After cooling to 0 °C overnight, the resulting solid was filtered, washed with ethyl ether and concentrated in vacuo to yield the di-quaternary salt as an off-white solid (1.046g, 92%):

¹H NMR (CD₃OD) δ 0.59 (t, 6H), 0.70-1.10 (m, 9H), 1.16 (t, 3H), 1.22-1.80 (m, 9H), 2.42 (s, 6H), 2.78 (d, 2H), 2.98 (s, 6H), 3.02 (s, 6H), 3.22-3.37 (m, 4H), 3.63-3.78 (m, 4H), 3.80 (s, 4H), 4.93 (s, 1H), 5.71 (s, 1H), 6.22 (dd, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.40 (d, 1H).

Step 4: Preparation of quaternary di-chloride salt

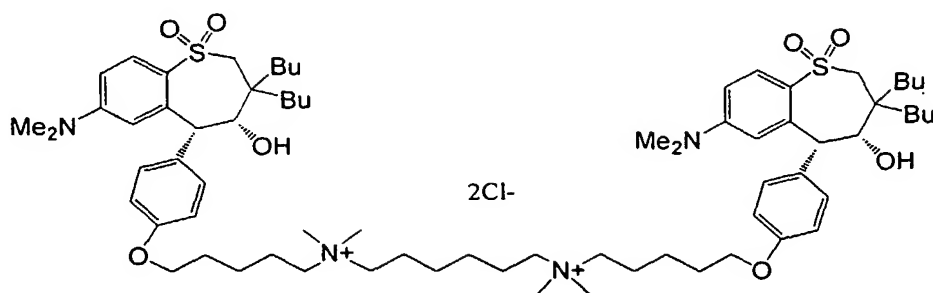
The iodobromosalt (obtained from Step 3) was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H₂O/acetonitrile to give the desired title compound as a white foamy solid (0.746g, 84%): mp 193.0-197.0 °C; ¹H NMR (CD₃OD) δ 0.59 (t, J = 6.0 Hz, 6H), 0.70-1.12 (m, 9H), 1.16 (t, J = 6.6 Hz, 3H), 1.24-1.90 (m, 9H), 2.50 (s, 6H), 2.78 (s, 2H), 3.08 (s, 6H), 3.11 (s, 6H), 3.24-3.50 (m, 4H), 3.68 (s, 2H), 3.81 (s, 2H), 4.16 (s, 4H), 5.02 (s, 1H), 5.72 (s, 1H), 6.19 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz,

SRL 6071
(C-3021/2)

450

2H), 7.46 (d, $J = 8.7$ Hz, 1H). HRMS. Calc'd for $C_{39}H_{67}N_3O_4SCl$: 708.4541. Found: 708.4598.

5 Example 1419



[4R-[4a,5a(4R*,5R*)]]-N,N'-bis[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N,N,N',N'-tetramethyl-1,6-hexanediaminium dichloride

The pentyl bromide intermediate (1.002g, 1.64 mmol, obtained from Example 1418, Step 1) and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100g, 0.580 mmol) in 5 mL of acetonitrile were placed in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N_2 , sealed, equipped with magnetic stirrer and heated to 50 °C. After 15 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give an off-white foamy solid (1.141g). The solid was dissolved in acetonitrile and precipitated with ethyl ether. After cooling to 0 °C, the solvent was decanted to yield a sticky off-white solid. This trituration method was repeated, and the resulting sticky solid was concentrated in vacuo to give the desired dibromide salt as an off-white foamy solid (0.843g, quantitative): 1H NMR ($CDCl_3$) δ 0.85 (m, 12H), 1.01-1.70 (m, 30H), 1.76-2.08 (m, 12H), 2.18 (t, $J =$

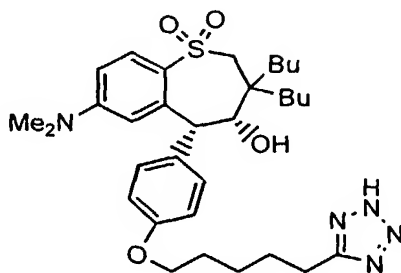
SRL 6071
(C-3021/2)

451

12.3 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.35 (s, 12H), 3.52 (br s, 6H), 3.72 (br s, 4H), 3.97 (br s, 4H), 4.08 (br s, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.51 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 7.8$ Hz, 4H), 7.38 (d, $J = 7.8$ Hz, 4H), 7.83 (d, $J = 8.7$ Hz, 2H). The dibromide salt was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H₂O/CH₃CN to give the desired title compound as a white foamy solid (0.676g, 86%): mp 178.0–182.0 °C; ¹H NMR (CDCl₃) δ 0.80–0.90 (m, 12H), 1.01–1.70 (m, 30H), 1.75–2.06 (m, 12H), 2.16 (t, $J = 12.9$ Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.33 (s, 12H), 3.49 (br s, 6H), 3.70 (br s, 4H), 3.96 (t, $J = 5.4$ Hz, 4H), 4.08 (s, 2H), 5.42 (s, 2H), 5.986 (s, 1H), 5.993 (s, 1H), 6.49 (d, $J = 9.0$ Hz, 1H), 6.50 (d, $J = 9.0$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 4H), 7.38 (d, $J = 8.1$ Hz, 4H), 7.84 (d, $J = 8.7$ Hz, 2 H). HRMS. Calc'd for C₃₆H₅₈N₂O₄S: 614.4118. Found: 614.4148.

20

Example 1420



25

(4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-(1H-tetrazol-5-yl)pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

Step 1: Preparation of pentyl bromide intermediate

SRL 6071
(C-3021/2)

452

To a stirred suspension of 1.01 g (25.4 mmol, 60% oil dispersion) of sodium hydride in 150 mL of DMF was added 9.0g (19.5 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in portions. After 30 minutes the reaction was cooled in a water bath (15 °C) and 4.48 g (195 mmol) of 1,5-dibromopropane was added. The reaction was stirred at ambient temperature for 1.5 hours and quenched with 50 mL of saturated NH_4Cl . The reaction was diluted with ethyl acetate, washed with water, brine, dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 25% ethyl acetate/hexanes afforded 10.17 g (85%) of the pentyl bromide intermediate as a colorless foam: mp 65-70 °C; ^1H NMR (CDCl_3) δ 0.84-0.98 (m, 6H), 1.04-1.52 (m, 10H), 1.58-1.65 (m, 3H), 1.82 (p, J = 6.8 Hz, 2H), 1.94 (p, J = 7.0 Hz, 2H), 2.12-2.26 (m, 1H), 2.82 (s, 6H), 3.06 (AB_q , J_{AB} = 15.2, 45.3 Hz, 2H), 3.44 (t, J = 6.7 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 6.15 (d, J = 2.7 Hz, 1H), 6.68 (dd, J = 2.5, 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.7 Hz, 1H).

25 Step 2: Preparation of pentyl nitrile intermediate

To a stirred solution of 378 mg (0.621 mmol) of the pentyl bromide intermediate (obtained from Step 1) in 1 mL of DMSO was added 37 mg (0.745 mmol) of sodium cyanide. The reaction was stirred at ambient temperature for 16 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo to afford 278 mg

SRL 6071
(C-3021/2)

453

(93% RPHPLC purity, ca. 75%) of the pentyl nitrile intermediate as a colorless foam: ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.02-1.21 (m, 1H), 1.21-1.52 (m, 19H), 1.58-1.92 (m, 7H), 2.16-2.28 (m, 1H), 2.41 (t, J = 6.9 Hz, 2H), 2.83 (s, 6H), 3.08 (AB_q , 15.0, 47.5 Hz, 2H), 4.01 (t, J = 6.2 Hz, 2H), 4.1 (s, 1H), 5.49 (s, 1H), 6.07 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 2.4, 8.7 Hz, 1H), 6.92 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.7 Hz, 1H). MS (ES, M^+H) m/e 555.

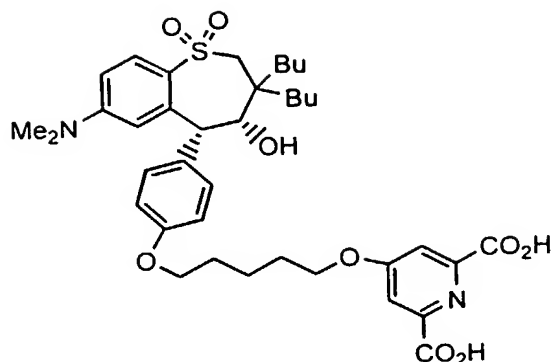
Step 3: Preparation of tetrazole

A solution of 275 mg (0.5 mmol) of the nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene was stirred with heating at 80 °C for 60 hours. The reaction was concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 226 mg of the desired title compound (75%) as a colorless foam: mp 80-85 °C; ^1H NMR (CDCl_3) δ 0.83-0.95 (m, 6H), 1.30-1.52 (m, 10H), 1.52-1.73 (m, 3H), 1.79-1.99 (m, 4H), 2.14-2.26 (m, 1H), 2.91 (s, 6H), 3.02-3.22 (m, 4H), 3.92-4.06 (m, 2H), 4.16 (s, 1H), 5.47 (s, 1H), 6.28 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 2.7, 8.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 8.7 Hz, 1H). HRMS Calc'd for $\text{C}_{32}\text{H}_{48}\text{N}_5\text{O}_4\text{S}$: 598.3427. Found: 598.3443.

30 Example 1421

SRL 6071
(C-3021/2)

454



(4R-cis)-4-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
1benzothiepin-5-yl]phenoxy]pentyl]oxy]-2,6-
pyridinecarboxylic acid

Step 1: Preparation of pentyl bromide intermediate

To a solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was add 6.0g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate:

¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Esterification of chelidamic acid

SRL 6071
(C-3021/2)

455

5 A solution of 10 g (54.6 mmol) of chelidamic acid, 23.0 g (120.12 mmol) of 1-(3-dimethyl amino propyl)-3 ethyl carbodiimide hydrochloride, 1.33 g (10.8 mmol) of 4-dimethyl amino pyridine, and 12.4 mL (120.12 mmol) of benzyl alcohol in 100 mL of DMF was stirred at ambient temperature overnight under N₂. DMF was removed in vacuo and the residue was extracted with methylene chloride, washed with 5% NaHCO₃, 5% acetic acid, H₂O, and brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give dibenzyl chelidamic ester: ¹H NMR (CDCl₃) δ 5.4 (s, 4H), 7.4 (m, 12H).

15 Step 3: Preparation of pyridinyl benzyl ester intermediate

A solution of 79 mg (1.972 mmol, 60% disp) of NaH and 0.716g (1.972 mmol) of dibenzyl chelidamic ester (obtained from Step 2) in 17.5 mL of DMF was stirred at ambient temperature for 1 hour. To the solution was added 1.0 g (1.643 mmol) of the pentyl bromide intermediate and the mixture was stirred under N₂ overnight at 40 °C. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pyridinyl dibenzyl ester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.0 (t, 2H), 4.1 (s, 1H), 5.4 (s, 4H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3-7.5 (m, 12H), 7.78 (s, 2H), 7.9 (d, 1H).

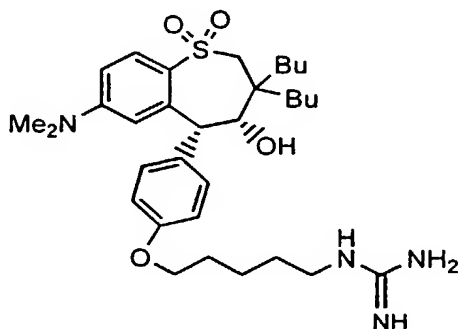
Step 4: Preparation of pyridinyl diacid

SRL 6071
(C-3021/2)

456

A suspension of 0.8813 g (0.99 mmole) of dibenzyl ester (obtained from Step 3) and 40 mg of 10% Pd/C in 35 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 143 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 15H), 1.9 (m, 4H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 4.1 (s, 3H), 4.3 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.78 (d, 1H), 7.82 (s, 2H). HRMS. Calc'd for C₃₈H₅₀N₂O₉S: 711.3315. Found: 711.3322. Anal. Calc'd for C₃₈H₅₀N₂O₉S: C, 64.20; H, 7.09; N, 3.94; S, 4.51. Found: C, 62.34; H, 6.97; N, 4.01; S, 4.48.

Example 1422



SRL 6071
(C-3021/2)

457

mmol) of sodium azide and a catalytic amount of sodium iodide. The reaction was stirred at ambient temperature for 64 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo to afford 155 mg (92% RPHPLC purity, about 76% yield) of the pentyl azide intermediate as a colorless foam. Sample was used without further purification: mp 45-50 °C; ^1H NMR (CDCl_3) δ 0.83-0.93 (m, 6H), 1.03-1.48 (m, 10H), 1.54-1.74 (m, 5H), 1.78-1.86 (m, 1H), 2.14-2.26 (m, 1H), 2.81 (s, 6H), 3.06 (AB_q , $J_{\text{AB}} = 15.0, 48.0$ Hz, 2H), 3.31 (t, $J = 6.3$ Hz, 2H), 3.98 (t, $J = 6.3$ Hz, 2H), 4.09 (s, 1H), 5.47 (s, 1H), 6.10 (d, $J = 1.8$ Hz, 1H), 6.63 (dd, $J = 2.7, 9.0$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H). MS (FAB, $\text{M}+\text{H}$) m/e 571.

Step 2: Preparation of pentyl amine intermediate

To a solution of 0.67 g (1.17 mmol) of the azide intermediate (obtained from Step 1) in 75 mL of ethanol was added 0.10 g of 10% palladium on carbon and the mixture shaken under 49 psi of hydrogen at ambient temperature for 3.5 hours. The reaction was filtered through celite and concentrated in vacuo to give 0.62 g (86% RPHPLC purity, ca. 84%) of pentyl amine intermediate as an off-white foam. The sample was used without further purification: mp 70-85 °C; ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.06-1.75 (m, 15H), 1.79-1.93 (m, 4H), 2.15-2.28 (m, 1H), 2.82 (s, 6H), 2.96-3.20 (m, 4H), 3.99 (t, $J = 6.0$ Hz, 2H), 4.04-4.14 (m, 1H), 5.49 (s, 1H), 6.00 (d, $J = 1.5$ Hz, 1H), 6.51 (d, $J = 9.0$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J =$

SRL 6071
(C-3021/2)

458

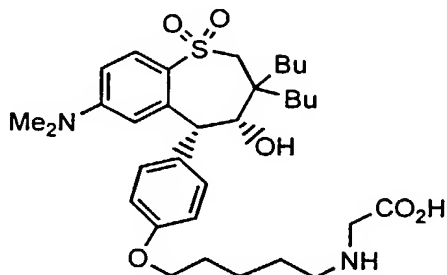
8.1 Hz, 2H), 7.90 (d, $J = 8.7$ Hz, 1H). MS (ES, M+H)
 m/e 545.

Step 3: Preparation of guanidine

5 To a stirred solution of 258 mg (0.474 mmol) of
pentyl amino intermediate (obtained from Step 2) and 81
mg (0.551 mmol) of 1H-pyrazole-1-carboxamide
hydrochloride in 1.5 mL of DMF was added 71 mg (0.551
10 mmol) of diisopropylethylamine. The reaction was
stirred at ambient temperature for 16 hours.
Purification by reversed phase chromatography (Waters-
Delta prep) using 60% water/acetonitrile afforded 120
mg (43%) of the desired title compound as colorless
foamy solid: mp 67.0-72.5 °C; ^1H NMR (CDCl_3) δ 0.89-0.93
15 (m, 6H), 1.05-1.17 (m, 1H), 1.26-1.90 (m, 16H), 2.07-
2.24 (m, 1H), 2.81 (s, 6H), 2.99-3.19 (m, 4H), 3.98 (br
s, 2H), 4.12 (s, 1H), 5.46 (s, 1H), 6.01 (d, $J = 2.1$
Hz, 1H), 6.51 (dd, $J = 2.1, 8.0$ Hz, 1H), 6.92 (d, $J =$
8.1 Hz, 2H), 7.41 (d, $J = 7.8$ Hz, 2H), 7.89 (d, $J = 8.7$
20 Hz, 1H). HRMS. Calc'd for $\text{C}_{32}\text{H}_{50}\text{N}_4\text{O}_4\text{S}$: 586.3552.
Found (M+H): 587.3620.

Example 1423

25



(4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-

SRL 6071
(C-3021/2)

459

benzothiepin-5-yl]phenoxy]pentyl]glycine

Step 1: Preparation of pentyl azide intermediate

5 To a solution of pentyl bromide intermediate (400
mg, 0.657 mmol, obtained from Example 1420, Step 1) in
dimethyl sulfoxide (20 mL) was added sodium azide (47
mg, 0.723 mmol, 1.1 eq), and the resulting clear
solution was stirred at 23 °C for 16h. The reaction
10 solution was diluted with 100 mL ethyl acetate, then
washed with water (2x 100 mL) and brine (1x 100 mL).
The organic layer was dried (MgSO₄) and concentrated in
vacuo to give 390 mg (quantitative) of pentyl azide
intermediate as a yellow oil: ¹H NMR (CDCl₃) δ 0.82-
0.90 (m, 7H), 1.05-1.56 (m, 12H), 1.59-1.71 (m, 3H),
15 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.82 (s,
6H), 3.08 (q, 2H), 3.44 (t, J = 7.7 Hz, 2H), 3.99 (t, J
= 7.7 Hz, 2H), 4.91 (br s, 1H), 5.47 (s, 1H), 6.13 (d,
J = 7.58 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 7.14 (ABq,
4H), 7.91 (d, J = 7.8 Hz, 1H).

Step 2: Preparation of amino ester intermediate

20 A suspension of pentyl azide intermediate (390 mg,
0.684 mmol, obtained from Step 1) and 100 mg of
palladium on carbon in ethanol (15 mL) was agitated
25 under an atmosphere of hydrogen gas (48 psi) for 4.5
hours. The ethanolic suspension was filtered through
celite and concentrated in vacuo to give a yellow oil.

The oil was immediately diluted with acetonitrile (15
mL), followed by the addition of triethylamine (0.156
30 g, 1.54 mmol, 2.25 eq) and bromo acetic acid benzyl
ester (0.212 g, 0.925 mmol, 1.35 eq). The reaction was
stirred at 23 °C for 48 hours. The reaction was
concentrated in vacuo, and the residue was dissolved in
ethyl acetate (20 mL) and washed with water (2x 20 mL)
35 and brine (1x 20 mL). The organic layer was dried

SRL 6071
(C-3021/2)

460

(MgSO₄) and dried in vacuo to give 420 mg (89%) of the amino ester intermediate as a yellow oil: ¹H NMR (CDCl₃) δ 0.82-0.90 (m, 6H), 1.05-1.56 (m, 14H), 1.58-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, J = 8.3 Hz, 1H), 2.75 (d, J = 7.83 Hz, 1H), 2.795 (s, 6H), 3.08 (q, 2H), 3.68-3.85 (m, 2H), 3.87-4.04 (m, 2H), 4.09 (s, 1H), 5.147 (s, 1H), 5.46 (s, 1H), 5.98 (d, J = 7.58, 1H), 6.50 (dd, 1H), 6.85-6.87 (m, 2H), 7.28-7.45 (m, 5H), 7.89 (d, J = 8.0 Hz, 1H). MS (ES) m/e 693.

Step 3: Preparation of acid

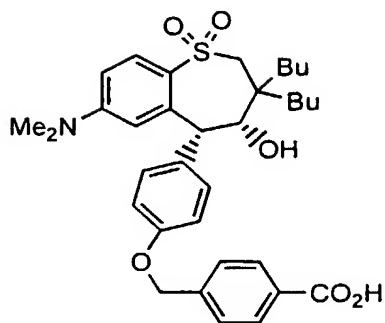
A suspension of benzyl ester intermediate (0.420g, 0.61 mmol, obtained from Step 2) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 16h. The suspension was filtered through celite, and concentrated in vacuo to give 0.330g of a yellow semi-solid. The material was triturated with diethyl ether and the remaining semi-solid was dried in vacuo to give 0.19 g (52%) of the desired title compound as a yellow semi solid: ¹H NMR (CDCl₃) δ 0.86 (br s, 7H), 1.0-1.72 (m, 18H), 1.79 (br s, 2H), 1.98 (s, 2H), 2.09-2.24 (m, 2H), 2.78 (s, 6H), 2.99 (q, 2H), 3.96 (bs, 2H), 4.08 (s, 1H), 5.46 (s, 1H), 5.97 (s, 1H), 6.40-6.49 (m, 1H), 7.14 (ABq, 4H), 7.85 (t, J = 7.93 Hz, 1H). MS (ES) m/e 603.

Example 1424

30

SRL 6071
(C-3021/2)

461



(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]benzoic acid

Step 1: Preparation of benzoate intermediate

To a solution of 0.53 g (1.15 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 10 mL dimethylformamide was added 35 mg (1.39 mmol) of 95% sodium hydride and stirred for 10 minutes.

To the reaction mixture was added 525 mg (2.29 mmol) methyl 4-(bromomethyl)benzoate and stirred for 16 hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.51 g (73%) of the benzoate

intermediate: ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.14-1.47 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.23 (m, 1H), 2.80 (s, 6H), 2.99 (d, $J = 15.1$ Hz, 1H), 3.15 (t, $J = 15.1$ Hz, 1H), 3.92 (s, 3H), 4.09-4.15 (m, 1H), 5.17 (s, 2H), 5.49 (s, 1H), 5.94 (d, $J = 2.2$ Hz, 1H), 6.50 (dd, $J = 8.9, 2.6$ Hz, 1H), 7.00 (d, $J = 8.7$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.93 (d, $J = 8.9$ Hz, 1H), 8.06 (d, $J = 8.5$ Hz, 2H).

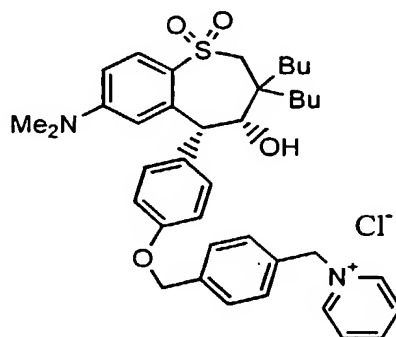
Step 2: Preparation of acid

SRL 6071
(C-3021/2)

462

A solution of 0.51 g (0.84 mmol) of the benzoate intermediate (obtained from Step 1) and 325 mg (2.53 mmol) of KOSi(CH₃)₃ (Aldrich) in 16 mL THF was stirred for 3.5 hours. The THF was evaporated, water added, extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.30 g (60%) of the desired title compound as a white solid: mp 156 - 159 °C; ¹H NMR (CDCl₃) δ 0.89-0.94 (m, 6H), 1.24-1.43 (m, 10H), 1.62-1.66 (m, 1H), 2.20-2.24 (m, 1H), 2.84 (s, 6H), 3.02 (d, *J* = 15.1 Hz, 1H), 3.17 (d, *J* = 15.1 Hz, 1H), 4.14 (s, 1H), 5.20 (s, 2H), 5.50 (s, 1H), 6.16 (s, 1H), 6.71 (d, *J* = 9.1 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 2H). HRMS. Calc'd for C₃₄H₄₄NO₆S: 594.2889. Found: 594.2913.

Example 1425



(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-pyridinium chloride

SRL 6071
(C-3021/2)

463

Step 1: Preparation of chlorobenzyl intermediate

A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25 °C under N₂ was treated with powdered K₂CO₃ (2.3 g, 16.3 mmol, 1.5 eq.) and α,α' -dichloro-*p*-xylene (6.7 g, 38.1 mmol, 3.5 eq.) and the resulting solution was stirred at 65 °C for 48 hours. The reaction mixture was cooled to 25 °C and concentrated to 1/5 of original volume. The residue was dissolved in EtOAc (150 mL) and washed with water (2 x 150 mL). The aqueous layer was extracted with EtOAc (2 x 150 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 150 mL). The combined extracts were dried (MgSO₄) and concentrated in vacuo to provide a yellow oil. Purification by flash chromatography (5.4 x 45 cm silica, 25-40% EtOAc/hexane) afforded the chlorobenzyl intermediate (4.7 g, 72%) as a white foam: ¹H NMR (CDCl₃) δ 0.89-0.94 (m, 6H), 1.12-1.48 (br m, 10H), 1.63 (m, 1H), 2.22 (m, 1H), 2.81 (s, 6H), 3.05 (ABq, *J* = 15.1 Hz, *J* = 50.0 Hz, 2H), 4.11 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 2H), 5.11 (s, 2H), 5.48 (s, 1H), 5.96 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, *J* = 8.9 Hz, 1H).

Step 2: Preparation of quaternary salt

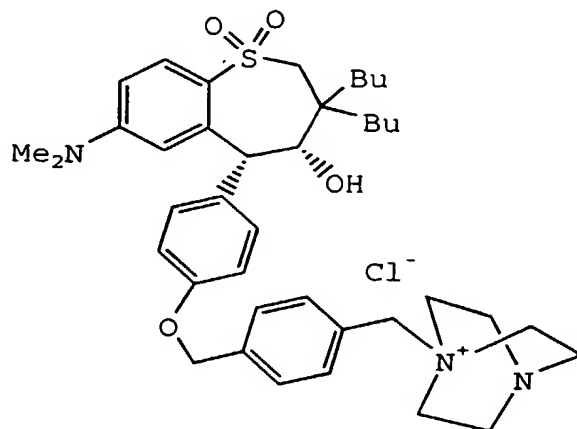
A solution of the chlorobenzyl intermediate (1.0 g, 1.7 mmol, obtained from Step 1) in acetonitrile (5 mL) at 25 °C under N₂ was treated with pyridine (5 mL) and stirred at 35 °C for 36 hours. The pale amber solution was cooled to 25 °C and concentrated in vacuo to give the desired title compound (1.08 g, 96%) as a

SRL 6071
(C-3021/2)

464

yellow solid: mp 154-156 °C; ¹H NMR (CDCl₃) δ 0.83 (m, 6H), 1.06-1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H), 2.71 (s, 6H), 3.02 (ABq, *J* = 15.1 Hz, *J* = 28.4 Hz, 2H), 4.09 (s, 1H), 5.00 (s, 2H), 5.38 (s, 1H), 5.91 (d, *J* = 2.4 Hz, 1H), 6.26 (s, 2H), 6.41 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, *J* = 7.7 Hz, 4H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 8.9 Hz, 2H), 7.93 (t, *J* = 6.8 Hz, 1H), 8.34 (t, *J* = 7.7 Hz, 1H), 8.58 (br s, 1H), 9.69 (d, *J* = 5.8 Hz, 2H);
HRMS. Calc'd for C₃₉H₄₉N₂O₄S: 641.3413. Found: 641.3425.

Example 1426



15

(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

20

Under N₂, a solution of 8.7 g (14.5 mmol) of the chlorobenzyl intermediate (obtained from a procedure similar to the one outlined in Example 1425, Step 1) in 60 mL of acetonitrile was added dropwise over a 30 min period to a solution of 2.9 g (26.2 mmol) of

25

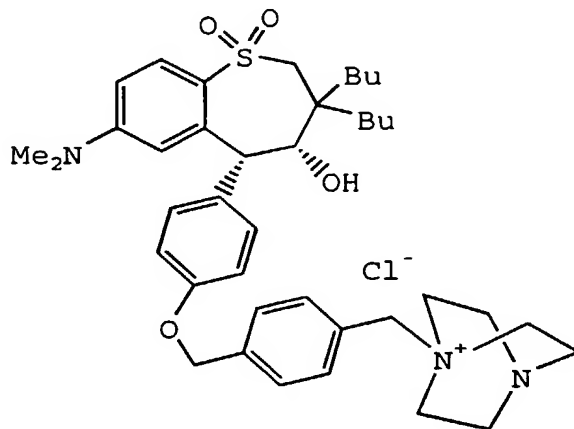
SRL 6071
(C-3021/2)

465

5 diazabicyclo[2.2.2]octane (DABCO) in 40 mL of
acetonitrile at 35°C; during the addition, a colorless
precipitate was formed. The slurry was stirred at 35°C
for an additional 2 h. The product was collected and
washed with 1 L of acetonitrile to give 9.6 g (93%) the
title compound as a colorless crystalline solid: mp
223-230°C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H),
1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81
(s, 6H), 3.06 (ABq, J = 15.1 Hz, J = 43.3 Hz, 2H), 3.16
10 (s, 6H), 3.76 (s, 6H), 4.11 (d, J = 7.7 Hz, 1H), 5.09
(s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49
(d, J = 8.9 Hz, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.26 (m,
1H), 7.44 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.4 Hz,
2H), 7.68 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.9 Hz,
15 1H); HRMS. Calc'd for C₄₀H₅₆N₃O₄S: 674.3992. Found:
674.4005.

Example 1426a

20



25

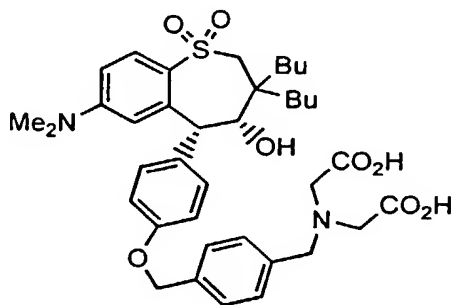
(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-
2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-
benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-
1-azoniabicyclo[2.2.2]octane chloride

SRL 6071
(C-3021/2)

466

A solution of the chlorobenzyl intermediate (4.6 g, 7.7 mmol, obtained from Example 1425, Step 1) in acetonitrile (100 mL) at 25°C under N₂ was treated with diazabicyclo[2.2.2]-octane (DABCO, 0.95 g, 8.5 mmol, 1.1 eq.) and stirred at 35°C for 2 hours, during which time a white solid precipitated out. The white solid was collected, washed with CH₃CN and recrystallized from CH₃OH/Et₂O to give the title compound (4.95 g, 91%) as a white solid: mp 223-230°C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, *J* = 15.1 Hz, *J* = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, *J* = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for C₄₀H₅₆N₃O₄S: 674.3992. Found: 674.4005.

Example 1427



4R-cis)-N-(Carboxymethyl)-N-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-

SRL 6071
(C-3021/2)

467

yl]phenoxy]methyl]phenyl]methyl]glycine

Step 1: Preparation of chlorobenzyl intermediate

To a stirred solution of 144 mg (3.59 mmol, 60%
5 disp) of NaH in 29 mL of DMF was added 1.5 g (3.26
mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-
hydrobenzothiepine-1,1-dioxide (obtained from Example
1402, Step 10), and the resulting solution was stirred
at ambient temperature for 45 min. To the solution was
10 added 7.13 g (40.75 mmol) of dichloro p-xylene, and the
mixture was stirred overnight. DMF was removed in
vacuo, and the residue was extracted with ethyl acetate
and washed with brine. The extract was dried over MgSO₄,
and the concentrated residue was purified by column
15 chromatography to give the chlorobenzyl intermediate: ¹H
NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2 (t,
1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.1 (d, 1H), 4.6 (s,
2H), 5.1 (s, 2H), 5.5 (s, 1H), 6.0 (s, 1H), 6.6 (d, 1H),
7.0 (d, 2H), 7.4 (m, 6H), 7.8 (d, 1H).

Step 2: Preparation of amino diester

A mixture of 1.03 g (1.72 mmol) of chlorobenzyl
intermediate (obtained from Step 1), 1.63 g (8.6 mmol)
of diethyl amino diacetate, and 0.72 g (8.6 mmol) of
25 NaHCO₃ in 30 mL of DMF was stirred at 100 °C for 6
hours. DMF was removed in vacuo and the residue was
extracted with ether and washed with brine. The extract
was dried over MgSO₄, and the concentrated residue was
purified by column chromatography to give amino diester
30 intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65
(m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55
(s, 4H), 3.95 (s, 2H), 4.1-4.2 (m, 5H), 5.05 (s, 2H),
5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H),
7.4 (s, 6H), 7.8 (d, 1H).

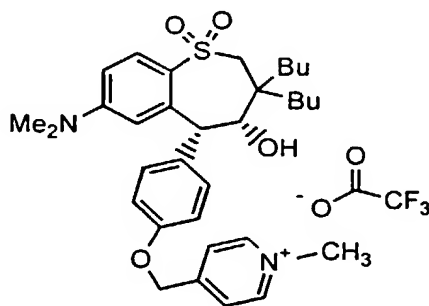
SRL 6071
(C-3021/2)

468

Step 3: Preparation of amino diacid

A solution of 0.863 g (1.15 mmol) of dibenzyl ester (obtained from Step 2) and 0.232 g (5.52 mmol) of LiOH in 30 mL of THF and 30 mL of water was stirred at 40 °C under N₂ for 4 hours. The reaction mixture was diluted with ether and washed with 1% HCl. The aqueous layer was extracted twice with ether, and the combined extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo to give the desired title compound as a solid: mp 175 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.5 (s, 4H), 3.9 (s, 2H), 4.1 (d, 1H), 5.1 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS. Calc'd for C₃₈H₅₀N₂O₈S: 695.3366. Found: 695.3359. Anal. Calc'd for C₃₈H₅₀N₂O₈S: C, 65.68; H, 7.25; N, 4.03; S, 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62.

Example 1428



(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium salt with trifluoroacetic acid (1:1)

SRL 6071
(C-3021/2)

469

Step 1: Preparation of picolyl intermediate

To a stirred solution of 12.0 g (26.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-

hydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 200 mL of DMF was added 1.4 g (60% oil dispersion, 35 mmol) of sodium hydride and the reaction stirred at ambient temperature for one hour.

5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride was treated with cold saturated NaHCO_3 solution and extracted with diethyl ether. The ethereal extracts were washed with brine, dried over MgSO_4 , and filtered.

The reaction was cooled in an ice bath and the solution of 4-picolyl chloride in diethyl ether was added. The reaction was stirred at ambient temperature for 17 hours. The reaction was quenched with 25 mL of saturated NH_4Cl , diluted with 600 mL ethyl acetate washed with 4X250 mL water, brine, dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-prep 500) using 60% ethyl acetate/hexanes afforded 11.05 g (77%) of the picolinyl intermediate as a colorless solid: mp 95-98

$^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.02-1.52 (m, 10H), 1.58-1.70 (m, 1H), 2.16-2.29 (m, 1H), 2.81 (s, 6H), 3.07 (AB_q , $J_{\text{AB}} = 15.3, 49.6$ Hz, 2H), 4.10 (d, $J = 7.5$ Hz, 1H), 5.15 (s, 2H), 5.50 (s, 1H), 5.94 (d, $J = 2.7$ Hz, 1H), 6.51 (dd, $J = 2.4, 8.7$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 2H), 7.39 (d, 6.0 Hz, 2H), 7.44 (s, $J = 8.7$ Hz, 2H), 7.89 (d, $J = 9.0$ Hz, 2H), 8.63 (dd, $J = 1.6, 4.8$ Hz, 2H).

Step 2: Preparation of quaternary salt

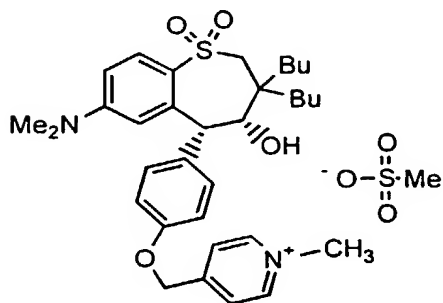
To a stirred solution of 0.41 g (0.74 mmol) of picolinyl intermediate (obtained from Step 1) in 10 mL of acetonitrile and 3 mL of dichloromethane was added

SRL 6071
(C-3021/2)

470

137 mg (0.97 mmol) of iodomethane. The reaction was stirred at ambient temperature for 16 hours, then concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60-55% water/acetonitrile afforded 0.304 g (60%) of the desired title compound as a colorless solid: mp 96-99 °C; ¹H NMR (CDCl₃) δ 0.85-0.95 (m, 6H), 1.03-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.27 (m, 1H), 2.84 (s, 6H), 3.09 (AB_q, J_{AB} = 15.0, 27.9 Hz, 2H), 4.11 (s, 1H), 4.46 (s, 3H), 5.37 (s, 2H), 5.50 (s, 1H), 6.07 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 2.5, 8.7 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 6.3 Hz, 2H), 8.80 (d, J = 6.6 Hz, 2H). HRMS Calc'd for C₃₃H₄₅N₂O₄S: 565.3100. Found: 565.3125.

Example 1429



(4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium, methanesulfonate (salt)

To a stirred solution of 6.5 g (11.8 mmol) of picolyl intermediate (obtained from Example 1428, Step

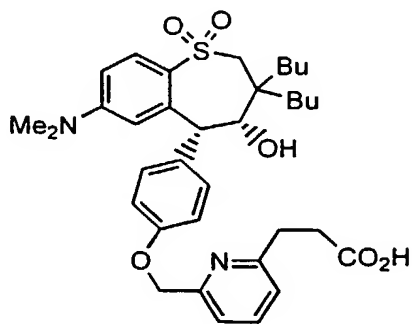
SRL 6071
(C-3021/2)

471

1) in 140 mL of acetonitrile heated at 70 °C was added
1.56 g (14.6 mmol) methanesulfonic acid methyl ester.
Heating was continued at 70 °C for 15 hours. The
reaction was cooled and diluted with 50 mL of ethyl
5 acetate. The solid was collected by vacuum filtration
to give 6.14 g (79%). The filtrate was concentrated in
vacuo and the residue crystallized from hot
acetonitrile to give 1.09 g (14%). A total of 7.23 g
(93%) of the desired title compound was obtained as an
10 off-white solid: mp 232-233.5 °C; ¹H NMR (CDCl₃) δ 0.66-
0.76 (m, 6H), 0.85-0.95 (m, 1H), 0.95-1.35 (m, 9H),
1.42- 1.54 (m, 1H), 1.95-2.22 (m, 1H), 2.50 (s, 1H),
2.56 (s, 3H), 2.63 (s, 6H), 2.91 (AB_q, J = 16.5, 24.0
Hz, 2H), 3.88 (s, 1H), 4.40 (s, 3H), 5.21 (s, 3H), 5.78
15 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 2.5, 8.7 Hz, 1H),
6.84 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H),
7.64 (d, J = 8.7 Hz, 1H), 8.0 (d, J = 6.6 Hz, 2H), 9.02
(d, J = 6.6 Hz, 2H). HRMS Calc'd for C₃₃H₄₅N₂O₄S:
565.3100. Found: 656.3087. Anal. Calc'd for
20 C₃₄H₄₈N₂O₇S₂: C, 61.79; H, 7.32; N, 4.24; S, 9.70.
Found: C, 61.38, H, 7.47; N, 4.22; S, 9.95.

Example 1430

25



SRL 6071
(C-3021/2)

472

(4R-cis)-6-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinepropanoic acid

5 Step 1: Preparation of picolinyll chloride intermediate

To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1g, 2.1 mmol, obtained from Example 1402, Step 10) in acetone (50 mL) was added anhydrous K₂CO₃ (0.45g, 3.2 mmol), tetrabutylammonium iodide (0.1g, 0.2 mmol) and 2,6-bischloromethylpyridine (1.2g, 10.8 mmol). The flask was equipped with nitrogen gas adapter and magnetic stirrer. The reaction was heated to reflux for overnight. After 18 hours, the reaction was diluted with ether and washed with water and brine (30 mL). The organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Chromatographic purification through silica gel, eluting with 25% EtOAc/Hexane gave 0.75 g (55%) of the picolyl chloride intermediate as an oil (0.70g, 55%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 4.10 (d, 2H), 4.65 (s, 2H), 5.20 (s, 2H), 5.45 (s, 1H), 5.95 (s, 1H), 6.50 (d, 1H), 7.0 (d, 2H), 7.35-7.50 (m, 4H), 7.70-7.85 (m, 2H).

Step 2: Preparation of pyridinyll malonate intermediate

Dibenzyl malonate (1.42g, 5.01 mmol) in DMF (20.0 mL) and sodium hydride (0.13g, 3.3 mmol) were placed in a dry three-neck flask. The flask was equipped with nitrogen gas adapter and magnetic stirrer. The picolyl chloride intermediate (1g, 1.67 mmol) was added and heated at 90°C for overnight. The reaction was cooled and extracted with 5% HCl with methylene chloride and washed with water (25 mL), and brine (50 mL). The

SRL 6071
(C-3021/2)

473

organic layers were dried over MgSO_4 , filtered and concentrated. The residue was purified by C-18 reversed phase column eluting with 50% acetonitrile/water and gave pyridinyl malonate intermediate as a white foamy solid (1g, 71%): ^1H NMR (CDCl_3) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.22 (d, 2H), 4.05 (d, 1H), 4.16 (t, 1H), 5.02 (s, 2H), 5.08 (s, 4H), 5.44 (s, 1H), 5.97 (s, 1H), 6.96-7.10 (m, 3H), 7.20-7.32 (m, 12H), 7.5 (t, 1H), 7.9 (d, 1H).

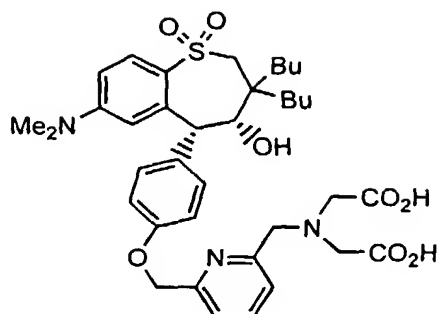
Step 3: Preparation of pyridinyl acid

The pyridinyl malonate intermediate (0.6g, 0.7 mmol, obtained from Step 2), THF/water (25.0 mL, 1:1) and lithium hydroxide monohydrate (0.14 g, 3.4 mmol) were placed in a 100 mL round-bottom flask. The reaction was stirred at ambient temperature overnight. After 18 hours, the reaction was extracted with 1% HCl and ether and then washed with water (20 mL) and brine (30 mL). The organic layers were dried over MgSO_4 , filtered and concentrated in vacuo gave the desired title compound as a white solid (0.44g, 90%): mp 105-107 °C; ^1H NMR (CDCl_3) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H), 3.05 (m, 2H), 3.10 (ABq, 2H), 3.22 (m, 2H), 4.05 (s, 1H), 5.30 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for $\text{C}_{35}\text{H}_{46}\text{N}_2\text{O}_6\text{S}$: 623.3155. Found: 623.3188.

Example 1431

SRL 6071
(C-3021/2)

474



(4R-cis)-N-(Carboxymethyl)-N-[[6-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinyl]methyl]glycine

Step 1: Preparation of pyridinyl diester intermediate

A mixture of diethyl aminodiacetate (8g, 68 mmol) and sodium carbonate (0.63g, 5.9 mmol) was treated with picolyl chloride intermediate (0.72g, 1.2 mmol, obtained from Example 1430, Step 1), and stirred at 160 °C for three hours. The reaction was cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by distillation in the Kugelrohr to give pyridinyl diester intermediate as a yellowish foamy solid (0.72g, 80%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 16H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.70 (s, 4H), 4.2-4.4 (m, 6H), 5.30 (s, 2H), 5.56 (s, 1H), 6.02 (s, 1H), 6.60 (d, 1H), 7.10 (d, 2H), 7.50 (m, 3H), 7.61 (d, 1H), 7.80 (t, 1H), 7.95 (d, 1H). HRMS. Calc'd for C₄₁H₅₇N₃O₈S: 752.3945. Found: 752.3948.

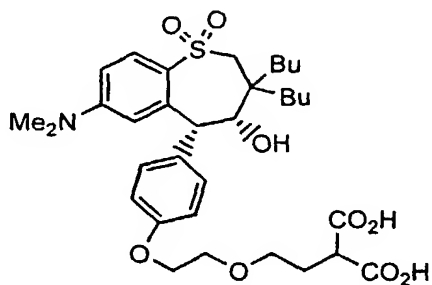
Step 2: Preparation of pyridinyl diacid

SRL 6071
(C-3021/2)

475

A mixture of pyridine-aminodiacetate intermediate (0.7g, 0.93 mmol, obtained from Step 1), and lithium hydroxide monohydrate (0.18 g, 4.5 mmol) in THF/ water (25.0 mL, 1:1) was stirred at 40 °C overnight (18 hours). The reaction mixture was diluted with ether and washed with 1% HCl, water (20 mL), and brine (30 mL). The organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the desired title compound as a white solid (0.44g, 90%): mp 153-155 °C; ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for C₃₇H₄₉N₃O₈S: 696.3319. Found: 696.3331.

Example 1432



(4S-cis)-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethyl]propanedioic acid

Step 1: Preparation of bromoethyl ether intermediate

SRL 6071
(C-3021/2)

476

To a stirred solution of 0.192 g (4.785 mmol, 60% disp) of NaH in 28 mL of DMF was added 2.0 g (4.35 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 30 min. To the solution was added 13.2 g (54.38 mmol) of bis(2-bromoethyl)ether, and stirring was continued at ambient temperature under N₂ overnight. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give bromoethyl ether intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6h), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.5 (t, 2H), 3.9 (m, 4H), 4.1 (d, 1H), 4.2 (d, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.95 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

Step 2: Preparation of diester intermediate

To a mixture of 94 mg (2.34 mmol, 60% disp) of NaH in 45 mL of THF and 15 mL of DMF at 0 °C was added 1.33 g (4.68 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min, followed by the addition of 0.95 g (1.56 mmol) of bromoethyl ether intermediate (obtained from Step 1). The mixture was stirred under N₂ at 80 °C overnight. Solvent was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the diester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2-2.3 (m, 3H), 2.8 (s, 6H), 3.0 (q, 2H), 3.6 (t, 2H), 3.7 (m,

SRL 6071
(C-3021/2)

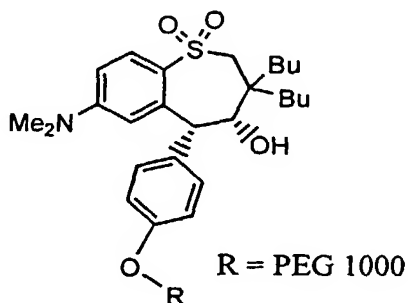
477

3H), 4.1 (m, 3H), 5.1 (s, 4H), 5.42 (s, 1H), 5.9 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3 (m, 10H), 7.4 (d, 2H), 7.9 (d, 1H).

5 Step 3: Preparation of diacid

A suspension of 0.761 g (0.935 mmol) of the diester intermediate (obtained from Step 2) and 35 mg of 10% Pd/C in 25 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 119.5 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.1 (q, 2H), 2.25 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.47 (q, 2H), 3.58 (s, 1H), 3.78 (t, 2H), 4.08 (d, 1H), 4.15 (t, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.55 (d, 1H), 6.98 (d, 2H), 7.42 (d, 2H), 7.8 (d, 1H). HRMS. Calc'd for C₃₃H₄₇NO₉S: 632.2893. Found: 632.2882. Anal. Calc'd for C₃₃H₄₇NO₉S: C, 62.54; H, 7.47; N, 2.21; S, 5.06. Found: C, 61.75; H, 7.56; N, 2.13; S, 4.92.

Example 1433



(4R-cis)-a-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-w-methoxypoly(oxy-1,2-ethanediyl)

SRL 6071
(C-3021/2)

478

Step 1: Preparation of monomethyl PEG mesylate intermediate

5 To a solution of 20 g of monomethyl ether PEG in
100 mL of methylene chloride was added 2.2 g (22 mmol)
of triethyl amine, and to the resulting solution at 0°C
was added dropwise 2.5 g (22 mmol) of methanesulfonyl
chloride. The resulting solution was stirred overnight
at ambient temperature, and the triethyl amine
10 hydrochloride was filtered off to give the monomethyl
PEG mesylate intermediate which was used in the next
Step without further purification and characterization.

15 Step 2: Preparation of polyethylene-linked
benzothiepine

A mixture of 38 mg (1.52 mmol 95%) of NaH and 0.7
g (1.52 mmol) of 5-(4'-hydroxyphenyl)-7-
(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide
(obtained from Example 1402, Step 10) in 5.5 mL of DMF
20 was stirred at ambient temperature under N₂ for 30 min.

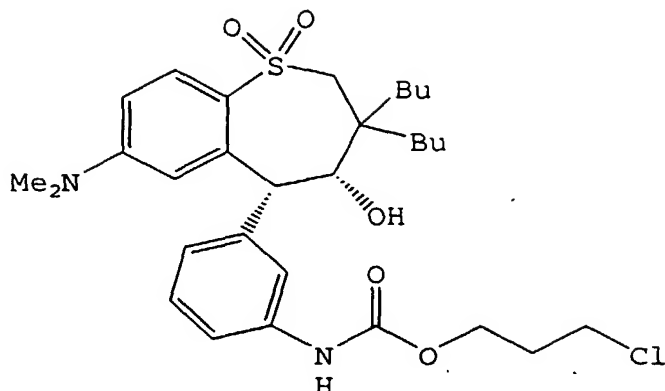
To the solution was added 0.55 g (0.51 mmol) of the
mesylate PEG intermediate (obtained from Step 1) in 5.5
mL of DMF, and the resulting solution was stirred
overnight under N₂ at 50 °C. DMF was removed in vacuo
25 and the residue was extracted with methylene chloride
and washed with brine. The extract was dried over MgSO₄,
and the concentrated residue was purified by column
chromatography to give the desired title compound as an
oil: ¹H NMR (CDCl₃) δ 0.9 (q, 6H), 1.05-1.65 (m, 11H),
30 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 4H),
3.5-3.85 (m, 95H), 4.1 (s, 1H), 4.15 (t, 2H), 5.5 (s,
1H), 6.05 (s, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d,
2H), 7.9 (d, 1H).

SRL 6071
(C-3021/2)

479

Example 1434

Preparation of:



5

The 3-aminobenzothiepine prepared in Step 5 of Example 1398 (0.380g, 0.828 mmol), sodium hydroxide (0.35 mL, 0.875 mmol, 10% in H₂O) and toluene (0.50 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and cooled to 0 °C. A solution of 3-chloropropyl chloroformate (1.440g, 1.10 mmol, 12% in CH₂Cl₂/ THF) was added. After 3.5 hrs, toluene (3.0 mL) was added, and the mixture was washed with H₂O (2x4 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20% EtOAc/hexane and concentrated *in vacuo* gave a white solid (0.269g, 56%). ¹H NMR (CDCl₃) δ

0.87-0.93 (m, 6H), 1.05-1.70 (m, 11H), 2.14 (t, J = 6.3 Hz, 2H), 2.15-2.25 (m, 1H), 2.81 (s, 6H), 3.07 (ABq, 2H), 3.64 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 7.5 Hz, 1H), 4.33 (t, J = 6.0 Hz, 2H), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.7 Hz, 1H), 6.65 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.34-7.39 (m, 2H), 7.54 (d, J = 7.2 Hz, 1H), 7.89 (d, 8.7 Hz, 1H). HRMS (M +

25

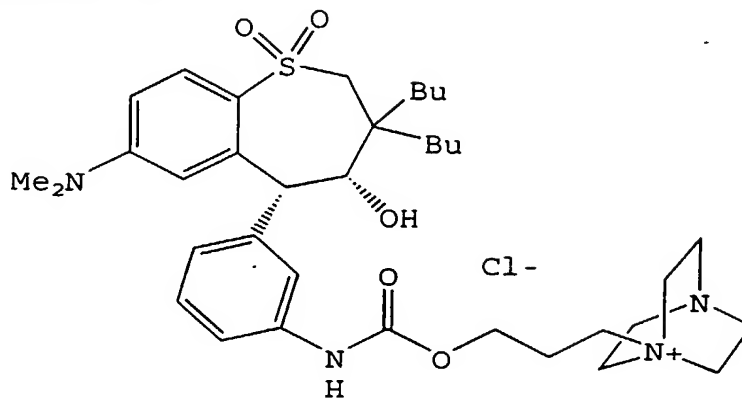
SRL 6071
(C-3021/2)

480

H). Calc'd for $C_{30}H_{44}N_2O_5SCl$: 579.2659. Found:
579.2691.

5 Example 1435

Preparation of:



10 1,4-Diazabicyclo(2.2.2)octane (0.0785g, 0.700
mmol) and acetonitrile (1.0 mL) were combined in a 10
mL round-bottom flask. The reaction flask was purged
with N_2 , equipped with magnetic stirrer, and heated to
37 °C. A solution of the product of Example 1434
15 (0.250g, 0.432 mmol) in acetonitrile (2.50 mL) was
added. After 2.5 hrs, 1,4-diazabicyclo(2.2.2)octane
(0.0200g, 0.178 mmol) was added. After 64 hrs, 1,4-
diazabicyclo(2.2.2)octane (0.0490g, 0.437 mmol) was
added. After 24 hrs, the reaction mixture was cooled
20 to R.T. and concentrated *in vacuo*. The crude product
was dissolved in acetonitrile (2.0 mL) and precipitated
with ethyl ether (10.0 mL). The precipitate was
filtered to yield a white solid. This trituration
method was repeated, followed by concentrated *in vacuo*
25 to give a white solid (0.185g, 62%). mp 218.0–225.0 °C;
 1H NMR (CD_3OD) δ 0.90 (m, 6H), 1.05–1.55 (m, 10H), 1.16
(t, J = 6.6 Hz, 2H), 1.78 (m, 1H), 2.12 (m, 3H), 2.76

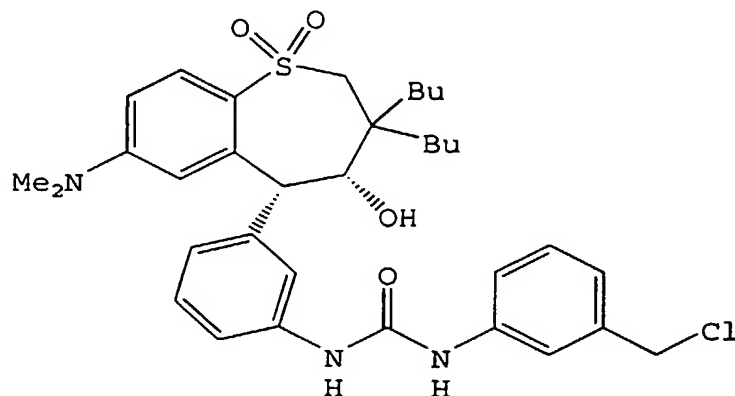
SRL 6071
(C-3021/2)

481

(s, 6H), 3.10 (m, 2H), 3.17 (t, $J = 7.2$ Hz, 6H), 3.30-3.50 (m, 8H), 4.10 (s, 1H), 4.21 (t, $J = 5.4$ Hz, 2H), 5.31 (s, 1H), 6.10 (s, 1H), 6.55 (d, $J = 7.2$ Hz, 1H), 7.25 (d, $J = 6.9$ Hz, 1H), 7.33-7.42 (m, 2H), 7.56 (s, 1H), 7.76 (d, $J = 9.0$ Hz, 1H). HRMS. Calc'd for $C_{36}H_{55}N_4O_5SCl$: 655.3893. Found: 655.3880.

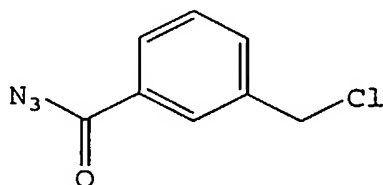
Example 1436

10 **Preparation of:**



Step 1. Preparation of:

15



20 3-Chloromethylbenzoyl chloride (2.25 mL/15.8 mmol) and acetone (8.0 mL) were combined in a 25 mL round-bottom flask. The reaction flask was cooled to 0°C, and an aqueous solution of sodium azide (1.56g in 5.50 mL/24.0 mmol) was added. After 1.5 hrs, the reaction mixture was poured into ice water (80.0 mL), extracted

SRL 6071
(C-3021/2)

482

with ethyl ether (2x25 mL), dried (MgSO₄), and concentrated *in vacuo* to give a colorless oil (2.660g, 86%). ¹H NMR (CDCl₃) δ 4.62 (s, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H).

Step 2.

3-Chloromethylbenzoyl azide (0.142g, 0.726 mmol) and toluene (2.0 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and heated to 110 °C. After 2 hrs, the reaction mixture was cooled to R.T, and the 3-aminobenzothiepine prepared in Step 5 of Example 1398 (0.365g, 0.796 mmol) was added. After 2.25 hrs, the mixture was heated to 50 °C. After 0.75 hrs, 3-chloromethylbenzoyl azide (0.025g, 0.128 mmol) was added, and the reaction mixture was heated to reflux. After 0.5 hrs, the reaction mixture was cooled to R.T. and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20-30% EtOAc/hexane and concentrated *in vacuo* gave a white foamy solid (0.309g, 62%). ¹H NMR (CDCl₃) δ 0.71 (t, J = 5.4 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H), 1.03-1.60 (m, 11H), 1.85 (d, 6.3 Hz, 1H), 2.27 (m, 1H), 2.76 (s, 6H), 3.15 (t, 2H), 4.17 (d, J = 6.6 Hz, 1H), 4.48 (s, 2H), 5.42 (s, 1H), 6.07 (s, 1H), 6.99 (d, J = 7.5 Hz), 7.18-7.26 (m, 2H), 7.30-7.41 (m, 3H), 7.63 (s, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 8.17 (s, 1H). HRMS (M + Li). Calculated for C₃₄H₄₄N₃O₄SClLi: 632.2901. Found: 632.2889.

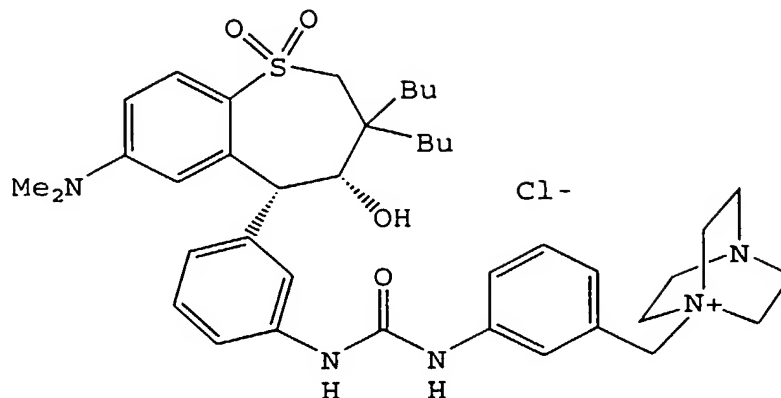
Example 1437

35

SRL 6071
(C-3021/2)

483

Preparation of:



5 1,4-Diazabicyclo(2.2.2)octane (0.157g, 1.40 mmol)
and acetonitrile (1.00 mL) were combined in a 10 mL
round-bottom flask. The reaction flask was purged with
N₂ and equipped with magnetic stirrer. A solution of the
product of Example 1436 (0.262g, 0.418 mmol) in
10 acetonitrile (2.70 mL) was added. After 2.5 hrs, a
white precipitate had had formed. Ethyl ether (6.0 mL)
was added, and the precipitate was filtered, washed
with ethyl ether, and dried in vacuo to yield a white
solid (0.250g, 80%). mp 246.0-248.0 °C; ¹H NMR (CD₃OD)
15 δ 0.88 (m, 6H), 1.03-1.55 (m, 10H), 1.76 (m, 1H), 2.11
(m, 1H), 2.74 (s, 6H), 3.11 (m, 8H), 3.37 (m, 6H), 4.12
(s, 1H), 4.39 (s, 2H), 5.31 (s, 1H), 6.11 (s, 1H), 6.52
(dd, J = 8.7, 1.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H),
7.23 (d, J = 6.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.47 (m,
20 2H), 7.58 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H). HRMS.
Calculated for C₄₀H₅₆N₅O₄SCl: 702.4053. Found:
702.4064. Anal. Calculated for C₄₀H₅₆N₅O₄SCl: C,
65.06; H, 7.64; N, 9.48; S, 4.34; Cl, 4.80. Found: C,
64.90; H, 7.77; N, 9.42; S, 4.16; Cl, 4.89.

25

SRL 6071
(C-3021/2)

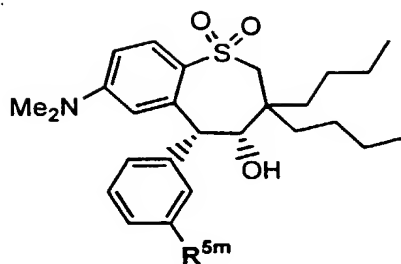
484

Examples 1438 - 1454

5 The compounds of Examples 1438 through 1454 can be prepared in accordance with one or more of the synthetic schemes previously disclosed in this application or using methods known to those skilled in the art.

SRL 6071
(C-3021/2)

485



R^{5m}

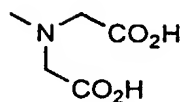
- 1438.
- 1439.
- 1440.
- 1441.
- 1442.
- 1443.
- 1444.
- 1445.
- 1446.

SRL 6071
(C-3021/2)

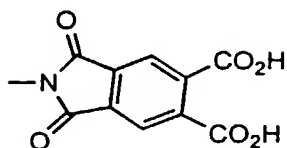
486

R^{5m}

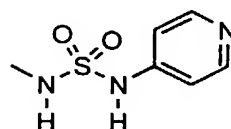
1446.



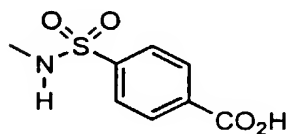
1447.



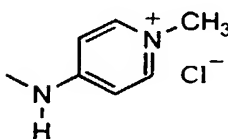
1448.



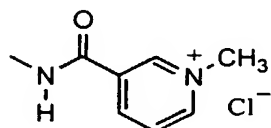
1449.



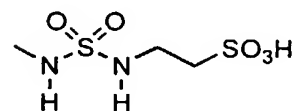
1450.



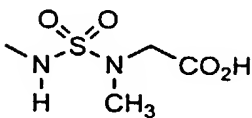
1451.



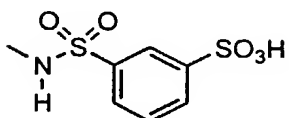
1452.



1453.



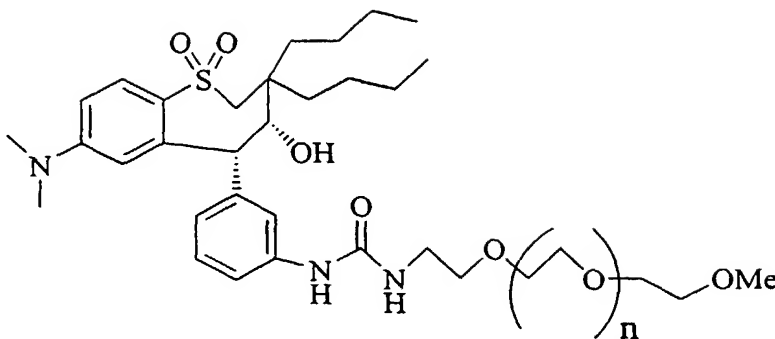
1454.



SRL 6071
(C-3021/2)

487

Example 1455



5

The 3-aminobenzothiepine of step 5 of Example 1398 (0.0165g/0.0360 mmol), M-NCO-5000 (0.150g/0.30 mmol) (Methoxy-PEG-NCO, MW 5000, purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), and CDCl_3 (0.7 mL) were combined in an 8 mm NMR tube. The tube was purged with N_2 . After 72 hrs, the reaction mixture was heated to 50 °C. After 24 hrs, an additional aliquot of the 3-aminobenzothiepine of step 5 of Example 1398 (0.0077g/0.017 mmol) was added. After 24 hrs, the reaction mixture was transferred to a 2 mL vial and evaporated to dryness with a N_2 purge. The resulting white solid was dissolved in hot ethyl ether (2.0 mL) and ethyl acetate (0.057 mL/4 drops), cooled to precipitate and filtered. This precipitation procedure was repeated until no starting material was detected in the precipitate (TLC: SiO_2 /80% EtOAc/hexanes). Concentrated *in vacuo* to give a white solid (0.0838g/51%). ^1H NMR (CDCl_3) δ 0.82-0.90 (m, 6H), 1.05-1.49 (m, 14H), 1.18 (t, J = 6.8 Hz, 2H), 1.59 (bt, 1H), 2.18 (bt, 1H), 2.34 (s, 2H), 2.78 (s, 6H), 3.04 (ABq, 2H), 3.35-3.80 (m, 625H), 4.09 (d, J = 7.2 Hz,

10

15

20

25

SRL 6071
(C-3021/2)

488

2H), 5.42 (s, 1H), 5.78 (s, 1H), 6.04 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 6.4, 3.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.31 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H). Mass spectroscopy
5 data also verified desired product.

BIOLOGICAL ASSAYS

10 The utility of the compounds of the present invention is shown by the following assays. These assays are performed *in vitro* and in animal models essentially using a procedure recognized to show the utility of the present invention.

15

In Vitro Assay of compounds that inhibit IBAT-mediated uptake of [¹⁴C]-Taurocholate (TC) in H14 Cells

Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded at 60,000
20 cells/well in 96 well Top-Count tissue culture plates for assays run within in 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours.

On the day of assay, the cell monolayer is gently
25 washed once with 100 µl assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose + 0.2% (w/v) fatty acid free bovine serum albumin- (FAF)BSA).

To each well 50 µl of a two-fold concentrate of test compound in assay buffer is added along with 50 µl of 6
30 µM [¹⁴C]-taurocholate in assay buffer (final concentration of 3 µM [¹⁴C]-taurocholate). The cell culture plates are incubated 2 hours at 37° C prior to gently washing each well twice with 100 µl 4° C

SRL 6071
(C-3021/2)

489

Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed once with 100 μ l 4° C PBS without (FAF)BSA. To each 200 μ l of liquid scintillation counting fluid is added, the plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

In Vitro Assay of compounds that inhibit uptake of [¹⁴C]-Alanine

The alanine uptake assay is performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

In Vivo Assay of compounds that inhibit Rat Ileal uptake of [¹⁴C]-Taurocholate into Bile

(See "Metabolism of 3 α ,7 β -dihydroxy-7 α -methyl-5 β -cholanoic acid and 3 α ,7 β -dihydroxy-7 α -methyl-5 β -cholanoic acid in hamsters" in Biochimica et Biophysica Acta 833 (1985) 196-202 by Une et al.)

Male wistar rats (200-300 g) are anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (1/8" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum.

A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum). 20 ml of warm Dulbecco's phosphate buffered saline, pH 6.5 (PBS) is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). The proximal

SRL 6071
(C-3021/2)

490

cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 min with warm PBS at 0.25 ml/min. Temperature of the gut segment is monitored continuously. At the start of the experiment, 2.0 ml of control sample ($[^{14}\text{C}]$ -taurocholate @ 0.05 $\mu\text{Ci}/\text{ml}$ with 5 mM cold taurocholate) is loaded into the gut segment with a 3 ml syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 ml/min for 21 min. Bile samples fractions are collected every 3 minute for the first 27 minutes of the procedure. After the 21 min of sample infusion, the ileal loop is washed out with 20 ml of warm PBS (using a 30 ml syringe), and then the loop is washed out for 21 min with warm PBS at 0.25 ml/min. A second perfusion is initiated as described above but this with test compound being administered as well (21 min administration followed by 21 min of wash out) and bile sampled every 3 min for the first 27 min. If necessary, a third perfusion is performed as above that typically contains the control sample.

Measurement of Hepatic Cholesterol Concentration
(HEPATIC CHOL)

Liver tissue was weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant was separated and dried under nitrogen. The residue was dissolved in isopropanol and the cholesterol content was measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., et al. (1974) *Clin. Chem.* 20, 470.

Measurement of Hepatic HMG CoA-Reductase Activity (HMG COA)

Hepatic microsomes were prepared by homogenizing

SRL 6071
(C-3021/2)

491

liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material was resuspended in buffer and an aliquot was assayed for HMG CoA reductase activity by incubating for 60 minutes at 37° C in the presence of ¹⁴C-HMG-CoA (Dupont-NEN). The reaction was stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant was separated, by thin-layer chromatography, and the spot corresponding to the enzyme product was scraped off the plate, extracted and radioactivity was determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) *J. Lipid Res.* 31, 2159).

15 Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)

Total serum cholesterol (SER.CHOL) was measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) was assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) were assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations were calculated as the difference between total and HDL cholesterol.

30 Measurement of Hepatic Cholesterol 7- α -Hydroxylase Activity (7 α -OHase)

Hepatic microsomes were prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material

SRL 6071
(C-3021/2)

492

was resuspended in buffer and an aliquot was assayed for cholesterol 7- α -hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent was evaporated and the residue was dissolved in acetonitrile/ methanol. The enzymatic product was separated by injecting an aliquot of the extract onto a C₁₈ reversed phase HPLC column and quantitating the eluted material using UV detection at 240nm. (Reference: Horton, J. D., et al. (1994) *J. Clin. Invest.* **93**, 2084).

Rat Gavage Assay

Male Wister rats (275-300g) are administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% Tween 80 in water) is administered once a day (9:00-10:0 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight. Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described below. Compound efficacy is determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

Measurement of Fecal Bile Acid Concentration (FBA)

Total fecal output from individually housed hamsters was collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram was weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue was dissolved in methanol and the amount of bile acid present was

SRL 6071
(C-3021/2)

493

measured enzymatically using the 3α -hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., et al. (1981) *Clin. Chem.* **27**, 1352).

5

[3 H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

10 Rabbit Ileal brush border membranes were prepared from frozen ileal mucosa by the calcium precipitation method describe by Malathi et al. (Reference: (1979) *Biochimica Biophysica Acta*, **554**, 259). The method for measuring taurocholate was essentially as described by Kramer et al. (Reference: (1992) *Biochimica Biophysica*
15 *Acta*, **1111**, 93) except the assay volume was 200 μ l instead of 100 μ l. Briefly, at room temperature a 190 μ l solution containing 2 μ M [3 H]-taurocholate(0.75 μ Ci), 20 mM tris, 100 mM NaCl, 100 mM mannitol pH 7.4 was incubated for 5 sec with 10 μ l of brush border membrane
20 vesicles (60-120 μ g protein). The incubation was initiated by the addition of the BBMV while vortexing and the reaction was stopped by the addition of 5 ml of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2
25 μ m pore) and an additional 5 ml wash with stop buffer.

Acyl-CoA;cholesterol Acyl Transferase (ACAT)

Hamster liver and rat intestinal microsomes were prepared from tissue as described previously
30 (Reference: (1980) *J. Biol. Chem.* **255**, 9098) and used as a source of ACAT enzyme. The assay consisted of a 2.0 ml incubation containing 24 μ M Oleoyl-CoA (0.05 μ Ci) in a 50 mM sodium phosphate, 2 mM DTT ph 7.4 buffer containing 0.25 % BSA and 200 μ g of microsomal
35 protein. The assay was initiated by the addition of

SRL 6071
(C-3021/2)

494

oleoyl-CoA. The reaction went for 5 min at 37° C and was terminated by the addition of 8.0 ml of chloroform/methanol (2:1). To the extraction was added 125 µg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction were separated by centrifugation after thorough vortexing. The chloroform phase was taken to dryness and then spotted on a silica gel 60 TLC plate and developed in hexane/ethyl ether (9:1). The amount of cholesterol ester formed was determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the TLC plate with a Packard instaimager.

Data from each of the noted compounds in the assays described above is as set forth in TABLES 5, 6, 7, and 8 as follows:

SRL 6071
(C-3021/2)

495

TABLE 5

| COMPOUND | IC50 uM* | In vitro % Inhibition of TC Uptake @ 100 uM # | % Inhibition of Alanine Uptake @ 100 uM # | % of Control Transport of TC in Rat Ileum @ 0.1mM # |
|-------------------------|-------------|---|---|---|
| Benzothiaze pine= | 2 | | 0 | 45.4 +/- 0.7 |
| 12 | | 25 | | |
| 3 | | 0 | | |
| 4a | | 3 | | |
| 5a | | 34 | | |
| 5b | 40 | | 0 | 72.9 ± 5.4 @ 0.5 mM |
| 4b | | 9 | | |
| 18 | | 6 | | |
| 14b | | 18 | | |
| 14a | | 13 | | |
| 13 | | 23 | | |
| 15 | 60 | | | |
| 19a | | 0 | | |
| 19b | | 15 | | |
| 8a | | 41 | | |
| Mixture of 8a and 8b | | 69 | | |
| Mixture of | 6 | | | |

SRL 6071
(C-3021/2)

496

| | | | | |
|--------------------------|-----|----|---------------------|--|
| 9a and 9b | | | | |
| 6a | 5 | | | |
| 6b | | 85 | | |
| 9a | 5 | | 0% @ 25 μ M | 53.7 +/- 3.9 |
| Mixture of 6a and 20 | 13 | | | |
| Mixture of 6d and 10a | 0.8 | | 14% @ 25 μ M | |
| 21a | | 37 | | |
| 21c | | 52 | | |
| 21b | | 45 | | |
| 6c | 2 | | 58.5 | 68.8 +/- 5.7 at 0.4 mM |
| 6d | 0.6 | | 77.7 | 16.1 +/- 1.1 @ 0.5 mM 30.2 +/- 0.9 @ 0.15 mM |
| 17 | | 10 | | |
| 7 | 50 | | 49.3 | |
| 10a | 7 | | 77.6 | 62.4 +/- 2.5 @ 0.2 mM |
| 10b | 15 | | 68.6 | |
| 25 | 0.1 | | 4% @ 10 μ M | 26.0 +/- 3.3 |
| 26 | 2 | | 31% @ 25 μ M | 87.9 +/- 1.5 |
| 27 | 5 | | 7% @ 20 μ M | |

SRL 6071
(C-3021/2)

497

| | | | | |
|----|------|-----------------|----------------------|--------------|
| 28 | 8 | | 31% @ 20 μ M | |
| 29 | | 88 @ 50 μ M | | |
| 30 | | 96 @ 50 μ M | | |
| 31 | | 41 @ 50 μ M | | |
| 37 | 3 | | 0% @ 5 μ M | |
| 38 | 0.3 | | 11% @ 5 μ M | 20.6 +/- 5.7 |
| 40 | | 49 @ 50 μ M | | |
| 41 | 2 | | 0% @ 20 μ M | |
| 42 | 1.5 | | | |
| 43 | 1.5 | | 16% @ 25 μ M | |
| 48 | 2 | | 22% @ 20 μ M | |
| 49 | 0.15 | | 21% @ 200 μ M | 21.2 +/- 2.7 |
| 57 | | 51 @ 50 μ M | | |
| 58 | | 20 @ 50 μ M | | |
| 59 | 70 | | | |
| 60 | 9 | | 59 | |
| 61 | 30 | | 175 | |
| 62 | 10 | | | |
| 63 | | 90 @ 6 μ M | | |

SRL 6071
(C-3021/2)

498

| | | | | |
|----|--|-----------------|--|--|
| 64 | | 100 @ 6 μ M | | |
|----|--|-----------------|--|--|

* In vitro Taurocholate Cell Uptake

Unless otherwise noted

5 = Comparative Example is Example No. 1 in WO 93/16055

SRL 6071
(C-3021/2)

499

TABLE 6

| Compound | TC-uptake | TC-uptake | TC-uptake | ACAT | ACAT |
|-------------------|----------------|---------------|-------------|------------|------------|
| | (H14 cells) | Ileal Loop | (BBMV) | (liver) | intestine |
| | IC(50) | EC(50) | IC(50) | IC(50) | IC(50) |
| COMP. EXAMPLE* | 1 μ M | 74 μ M | 3 μ M | 20 μ M | 20 μ M |
| 6d | 0.6 μ M | 31 μ M | 1.5 μ M | 25 μ M | 20 μ M |
| * 38 | 0.3 μ M | 12 μ M | 2 μ M | 15 μ M | N.D. |
| 49 | 0.1 μ M | 12 μ M | N.D. | 6 μ M | N.D. |
| 25 | 0.1 μ M | 20 μ M | 0.8 μ M | 8 μ M | 8 μ M |

Comparative Example is Example No. 1 in WO 93/16055

SRL 6071
(C-3021/2)

500

| TABLE 7 EFFICACY OF COMPOUND NO. 25 IN CHOLESTEROL-FED HAMSTERS | | | |
|--|---|--|------------------------|
| PARAMETER | CONTROL | 4% CHOLES- TYRAMINE | 0.2% CPD. NO. 25 |
| WEIGHT (G) | (mean \pm SEM, *p<0.05, A-Student's t, B-Dunnett's) | | |
| day 1 | 117 (2) | 114 (6) | 117 (5) |
| day 14 | 127 (3) | 127 (3) | 132 (4) |
| LIVER WEIGHT (G) | 5.4 (0.3) | 4.9 (0.4) | 5.8 (0.2) |
| SER. CHOL (mg%) | 143 (7) | 119 (4) *A, B | 126 (2) *A, B |
| HDL-CHOL (mg%) | 89 (4) | 76 (3) *A, B | 76 (1) *A, B |
| VLDL + LDL | 54 (7) | 42 (3) *A | 50 (3) |
| TGI (mg%) | 203 (32) | 190 (15) | 175 (11) |
| HEPATIC CHOL (mg/g) | 2.5 (0.3) | 1.9 (0.1) *A, B | 1.9 (0.1) *A, B |
| HMG COA (pm/mg/min.) | 15.8 (7.6) | 448.8 (21.6) * A, B | 312.9 (37.5) *A , B |
| 7 α -OHase (pm/mg/min.) | 235.3 (25.1 | | |
| 24 HR. FECAL Wt (G) |) | 357.2 (28.3) * | 291.0 (6.0) *A |
| FBA (mM/24H/100g) | 2.3 (0.1) | A, B | 2.4 (0.04) |
| | 6.2 (0.8) | 2.7 (0.1) *A, B 12.3 (1.5) *A, B | 11.9 (0.5) *A, B |

SRL 6071
(C-3021/2)

501

| TABLE 8 EFFICACY OF COMPOUND NO. 25 IN RAT ALZET MINIPUMP MODEL | | |
|--|---|---------------------------|
| PARAMETER | CONTROL | 20 MPL/DAY CPD. NO. 25 |
| WEIGHT (G) | (mean \pm SEM, *p<0.05, A-Student's t, B-Dunnett's) | |
| day 1 | 307 (4) | 307 (3) |
| day 8 | 330 (4) | 310 (4) *A,B |
| LIVER WEIGHT (G) | 15.5 (0.6) | 14.6 (0.4) |
| SER.CHOL(mg%) | 85 (3) | 84 (3) |
| HEPATIC CHOL(mg/g) | 21 (0.03) | 2.0 (0.03) |
| HMG COA pm/mg/min | 75.1 (6.4) | 318.0 (40.7) *A,B |
| 7a-OHase (pm/mg/min) | 281.9 (13.9) | 535.2 (35.7) *A,B |
| 24 HR. FECAL WT (G) | 5.8 (0.1) | 5.7 (0.4) |
| FBA (mM/24H/100g) | 17.9 (0.9) | 39.1 (4.5) *A,B |

Additional *in vitro* taurocholate uptake tests were conducted in the following compounds listed in Table 9.

SRL 6071
(C-3021/2)

502

Table 9
Biological Data for Some Compounds
of the Present Invention

5

| Compound Number | Human TC IC ₅₀ (μ M) | Alanine Uptake Percent Inhibition @ μ M |
|-----------------|--|--|
| 101 | | 0 @ 1.0 |
| 102 | 0.083 | |
| 103 | | 13 @ 0.25 |
| 104 | 0.0056 | |
| 105 | 0.6 | |
| 106 | 0.8 | |
| 107 | | 14.0 @ 0.063 |
| 108 | 0.3 | |
| 109 | | 2.0 @ 0.063 |
| 110 | 0.09 | |
| 111 | 2.5 | |
| 112 | 3.0 | |
| 113 | 0.1 | |
| 114 | 0.19 | |
| 115 | 8.0 | |
| 116 | 0.3 | |
| 117 | | 12.0 @ 0.625 |
| 118 | 0.4 | |
| 119 | 1.3 | |
| 120 | | 34.0 @ 5.0 |
| 121 | 0.068 | |
| 122 | 1.07 | |
| 123 | 1.67 | |
| 124 | | 14.0 @ 6.25 |
| 125 | 18.0 | |
| 126 | | 18 @ 1.25 |
| 127 | 0.55 | |
| 128 | 0.7 | |
| 129 | 0.035 | |
| 131 | 1.28 | |
| 132 | | 5.4 @ 0.063 |
| 133 | 16.0 | |
| 134 | 0.3 | |
| 135 | 22.0 | |
| 136 | 0.09 | |
| 137 | 2.4 | |
| 138 | 3.0 | |
| 139 | >25.0 | |
| 140 | | |

SRL 6071
(C-3021/2)

503

| | | |
|------|--------|-------------|
| 141 | | |
| 142 | 0.5 | |
| 143 | 0.03 | |
| 144 | 0.053 | |
| 262 | 0.07 | |
| 263 | 0.7 | |
| 264 | 0.2 | |
| 265 | 2.0 | |
| 266 | 0.5 | |
| 267 | 0.073 | |
| 268 | 0.029 | |
| 269 | 0.08 | |
| 270 | 0.12 | |
| 271 | 0.07 | |
| 272 | 0.7 | |
| 273 | 1.9 | |
| 274 | 0.18 | |
| 275 | | 5.0 @ 0.25 |
| 276 | 0.23 | |
| 277 | 0.04 | |
| 278 | 3.0 | |
| 279 | 0.4 | |
| 280 | 0.18 | |
| 281 | 0.019 | |
| 282 | 0.021 | |
| 283 | 0.35 | |
| 284 | 0.08 | |
| 285 | | |
| 286 | 19.0 | |
| 287 | 4.0 | |
| 288 | | 10.0 @ 6.25 |
| 289 | 0.23 | |
| 290 | 0.054 | |
| 291 | 0.6 | |
| 292 | 0.046 | |
| 293 | 1.9 | |
| 294 | 0.013 | |
| 295 | 1.3 | |
| 296 | 1.6 | |
| 1000 | | |
| 1001 | | |
| 1002 | | |
| 1003 | | |
| 1004 | | |
| 1005 | 0.0004 | |
| 1006 | 0.001 | |
| 1007 | 0.001 | |
| 1008 | 0.001 | |
| 1009 | 0.001 | |

SRL 6071
(C-3021/2)

504

| | | |
|------|--------|--|
| 1010 | 0.001 | |
| 1011 | 0.001 | |
| 1012 | 0.0015 | |
| 1013 | 0.002 | |
| 1014 | 0.002 | |
| 1015 | 0.002 | |
| 1016 | 0.002 | |
| 1017 | 0.002 | |
| 1018 | 0.002 | |
| 1019 | 0.002 | |
| 1020 | 0.002 | |
| 1021 | 0.002 | |
| 1022 | 0.002 | |
| 1023 | 0.002 | |
| 1024 | 0.002 | |
| 1025 | 0.002 | |
| 1026 | 0.002 | |
| 1027 | 0.002 | |
| 1028 | 0.002 | |
| 1029 | 0.002 | |
| 1030 | 0.002 | |
| 1031 | 0.002 | |
| 1032 | 0.002 | |
| 1033 | 0.002 | |
| 1034 | 0.002 | |
| 1035 | 0.002 | |
| 1036 | 0.002 | |
| 1037 | 0.0022 | |
| 1038 | 0.0025 | |
| 1039 | 0.0026 | |
| 1040 | 0.003 | |
| 1041 | 0.003 | |
| 1042 | 0.003 | |
| 1043 | 0.003 | |
| 1044 | 0.003 | |
| 1045 | 0.003 | |
| 1046 | 0.003 | |
| 1047 | 0.003 | |
| 1048 | 0.003 | |
| 1049 | 0.003 | |
| 1050 | 0.003 | |
| 1051 | 0.003 | |
| 1052 | 0.003 | |
| 1053 | 0.003 | |
| 1054 | 0.003 | |
| 1055 | 0.003 | |
| 1056 | 0.003 | |
| 1057 | 0.003 | |
| 1058 | 0.003 | |

SRL 6071
(C-3021/2)

505

| | | |
|------|--------|--|
| 1059 | 0.003 | |
| 1060 | 0.0036 | |
| 1061 | 0.004 | |
| 1062 | 0.004 | |
| 1063 | 0.004 | |
| 1064 | 0.004 | |
| 1065 | 0.004 | |
| 1066 | 0.004 | |
| 1067 | 0.004 | |
| 1068 | 0.004 | |
| 1069 | 0.004 | |
| 1070 | 0.004 | |
| 1071 | 0.004 | |
| 1072 | 0.004 | |
| 1073 | 0.004 | |
| 1074 | 0.004 | |
| 1075 | 0.0043 | |
| 1076 | 0.0045 | |
| 1077 | 0.0045 | |
| 1078 | 0.0045 | |
| 1079 | 0.005 | |
| 1080 | 0.005 | |
| 1081 | 0.005 | |
| 1082 | 0.005 | |
| 1083 | 0.005 | |
| 1084 | 0.005 | |
| 1085 | 0.005 | |
| 1086 | 0.005 | |
| 1087 | 0.005 | |
| 1088 | 0.0055 | |
| 1089 | 0.0057 | |
| 1090 | 0.006 | |
| 1091 | 0.006 | |
| 1092 | 0.006 | |
| 1093 | 0.006 | |
| 1094 | 0.006 | |
| 1095 | 0.006 | |
| 1096 | 0.006 | |
| 1097 | 0.006 | |
| 1098 | 0.006 | |
| 1099 | 0.0063 | |
| 1100 | 0.0068 | |
| 1101 | 0.007 | |
| 1102 | 0.007 | |
| 1103 | 0.007 | |
| 1104 | 0.007 | |
| 1105 | 0.007 | |
| 1106 | 0.0073 | |
| 1107 | 0.0075 | |

SRL 6071
(C-3021/2)

506

| | | |
|------|--------|--|
| 1108 | 0.0075 | |
| 1109 | 0.008 | |
| 1110 | 0.008 | |
| 1111 | 0.008 | |
| 1112 | 0.008 | |
| 1113 | 0.009 | |
| 1114 | 0.009 | |
| 1115 | 0.0098 | |
| 1116 | 0.0093 | |
| 1117 | 0.01 | |
| 1118 | 0.01 | |
| 1119 | 0.01 | |
| 1120 | 0.01 | |
| 1121 | 0.01 | |
| 1122 | 0.011 | |
| 1123 | 0.011 | |
| 1124 | 0.011 | |
| 1125 | 0.012 | |
| 1126 | 0.013 | |
| 1127 | 0.013 | |
| 1128 | 0.017 | |
| 1129 | 0.018 | |
| 1130 | 0.018 | |
| 1131 | 0.02 | |
| 1132 | 0.02 | |
| 1133 | 0.02 | |
| 1134 | 0.02 | |
| 1135 | 0.021 | |
| 1136 | 0.021 | |
| 1137 | 0.021 | |
| 1138 | 0.022 | |
| 1139 | 0.022 | |
| 1140 | 0.023 | |
| 1141 | 0.023 | |
| 1142 | 0.024 | |
| 1143 | 0.027 | |
| 1144 | 0.028 | |
| 1145 | 0.029 | |
| 1146 | 0.029 | |
| 1147 | 0.029 | |
| 1148 | 0.03 | |
| 1149 | 0.03 | |
| 1150 | 0.03 | |
| 1151 | 0.031 | |
| 1152 | 0.036 | |
| 1153 | 0.037 | |
| 1154 | 0.037 | |
| 1155 | 0.039 | |
| 1156 | 0.039 | |

SRL 6071
(C-3021/2)

507

| | | |
|------|-------|-----------|
| 1157 | 0.04 | |
| 1158 | 0.06 | |
| 1159 | 0.06 | |
| 1160 | 0.062 | |
| 1161 | 0.063 | |
| 1162 | 0.063 | |
| 1163 | 0.09 | |
| 1164 | 0.093 | |
| 1165 | 0.11 | |
| 1166 | 0.11 | |
| 1167 | 0.12 | |
| 1168 | 0.12 | |
| 1169 | 0.12 | |
| 1170 | 0.13 | |
| 1171 | 0.14 | |
| 1172 | 0.14 | |
| 1173 | 0.15 | |
| 1174 | 0.15 | |
| 1175 | 0.17 | |
| 1176 | 0.18 | |
| 1177 | 0.18 | |
| 1178 | 0.19 | |
| 1179 | 0.19 | |
| 1180 | 0.2 | |
| 1181 | 0.22 | |
| 1182 | 0.25 | |
| 1183 | 0.28 | |
| 1184 | 0.28 | |
| 1185 | 0.28 | |
| 1186 | 0.3 | |
| 1187 | 0.32 | |
| 1188 | 0.35 | |
| 1189 | 0.35 | |
| 1190 | 0.55 | |
| 1191 | 0.65 | |
| 1192 | 1.0 | |
| 1193 | 1.0 | |
| 1194 | 1.6 | |
| 1195 | 1.7 | |
| 1196 | 2.0 | |
| 1197 | 2.2 | |
| 1198 | 2.5 | |
| 1199 | 4.0 | |
| 1200 | 6.1 | |
| 1201 | 8.3 | |
| 1202 | 40.0 | |
| 1203 | | 0 @ 0.063 |
| 1204 | 0.05 | |
| 1205 | 0.034 | |

SRL 6071
(C-3021/2)

508

| | | |
|------|-------|-----------|
| 1206 | 0.035 | |
| 1207 | 0.068 | |
| 1208 | 0.042 | |
| 1209 | | 0 @ 0.063 |
| 1210 | 0.14 | |
| 1211 | 0.28 | |
| 1212 | 0.39 | |
| 1213 | 1.7 | |
| 1214 | 0.75 | |
| 1215 | 0.19 | |
| 1216 | 0.39 | |
| 1217 | 0.32 | |
| 1218 | 0.19 | |
| 1219 | 0.34 | |
| 1220 | 0.2 | |
| 1221 | 0.041 | |
| 1222 | 0.065 | |
| 1223 | 0.28 | |
| 1224 | 0.33 | |
| 1225 | 0.12 | |
| 1226 | 0.046 | |
| 1227 | 0.25 | |
| 1228 | 0.038 | |
| 1229 | 0.049 | |
| 1230 | 0.062 | |
| 1231 | 0.075 | |
| 1232 | 1.2 | |
| 1233 | 0.15 | |
| 1234 | 0.067 | |
| 1235 | 0.045 | |
| 1236 | 0.05 | |
| 1237 | 0.07 | |
| 1238 | 0.8 | |
| 1239 | 0.035 | |
| 1240 | 0.016 | |
| 1241 | 0.047 | |
| 1242 | 0.029 | |
| 1243 | 0.63 | |
| 1244 | 0.062 | |
| 1245 | 0.32 | |
| 1246 | 0.018 | |
| 1247 | 0.017 | |
| 1248 | 0.33 | |
| 1249 | 10.2 | |
| 1250 | 0.013 | |
| 1251 | 0.62 | |
| 1252 | 29. | |
| 1253 | 0.3 | |
| 1254 | 0.85 | |

SRL 6071
(C-3021/2)

509

| | | |
|------|-------|--|
| 1255 | 0.69 | |
| 1256 | 0.011 | |
| 1257 | 0.1 | |
| 1258 | 0.12 | |
| 1259 | 16.5 | |
| 1260 | 0.012 | |
| 1261 | 0.019 | |
| 1262 | 0.03 | |
| 1263 | 0.079 | |
| 1264 | 0.21 | |
| 1265 | 0.24 | |
| 1266 | 0.2 | |
| 1267 | 0.29 | |
| 1268 | 0.035 | |
| 1269 | 0.026 | |
| 1270 | 0.026 | |
| 1271 | 0.011 | |
| 1272 | 0.047 | |
| 1273 | 0.029 | |
| 1274 | 0.028 | |
| 1275 | 0.024 | |
| 1276 | 0.029 | |
| 1277 | 0.018 | |
| 1278 | 0.017 | |
| 1279 | 0.028 | |
| 1280 | 0.76 | |
| 1281 | 0.055 | |
| 1282 | 0.17 | |
| 1283 | 0.17 | |
| 1284 | 0.011 | |
| 1285 | 0.027 | |
| 1286 | 0.068 | |
| 1287 | 0.071 | |
| 1288 | 0.013 | |
| 1289 | 0.026 | |
| 1290 | 0.017 | |
| 1291 | 0.013 | |
| 1292 | 0.025 | |
| 1293 | 0.019 | |
| 1294 | 0.011 | |
| 1295 | 0.014 | |
| 1296 | 0.063 | |
| 1297 | 0.029 | |
| 1298 | 0.018 | |
| 1299 | 0.012 | |
| 1300 | 1.0 | |
| 1301 | 0.15 | |
| 1302 | 1.4 | |
| 1303 | 0.26 | |

SRL 6071
(C-3021/2)

510

| | | |
|------|--------|---------------|
| 1304 | 0.25 | |
| 1305 | 0.25 | |
| 1306 | 1.2 | |
| 1307 | 3.1 | |
| 1308 | 0.04 | |
| 1309 | 0.24 | |
| 1310 | 1.16 | |
| 1311 | 3.27 | |
| 1312 | 5.0 | |
| 1313 | 6.1 | |
| 1314 | 0.26 | |
| 1315 | 1.67 | |
| 1316 | 3.9 | |
| 1317 | 21.0 | |
| 1318 | | |
| 1319 | | 11.0 @ 0.25 |
| 1320 | | |
| 1321 | | 11.1 @ 5.0 |
| 1322 | | 3.0 @ 0.0063 |
| 1323 | | 4.0 @ 0.0063 |
| 1324 | | 43.0 @ 0.0008 |
| 1325 | | 1.0 @ 0.0063 |
| 1326 | | 36.0 @ 0.0008 |
| 1327 | | 3.0 @ 0.0063 |
| 1328 | | 68.0 @ 0.0063 |
| 1329 | | 2.0 @ 0.0063 |
| 1330 | | 9.0 @ 0.0063 |
| 1331 | | 57.0 @ 0.0008 |
| 1332 | | 43.0 @ 0.0008 |
| 1333 | | 0 @ 0.0063 |
| 1334 | | 50.0 @ 0.0008 |
| 1335 | | 38.0 @ 0.0008 |
| 1336 | | 45.0 @ 0.0008 |
| 1337 | | 0 @ 0.0063 |
| 1338 | | 1.0 @ 0.25 |
| 1339 | | 0 @ 0.063 |
| 1340 | | 9.0 @ 0.063 |
| 1341 | | 1.0 @ 0.063 |
| 1342 | | 1.0 @ 0.063 |
| 1343 | | |
| 1344 | | |
| 1345 | | 13.0 @ 0.25 |
| 1346 | | |
| 1347 | 0.0036 | |
| 1348 | | |
| 1349 | | |
| 1350 | | |
| 1351 | 0.44 | |
| 1352 | 0.10 | |

SRL 6071
(C-3021/2)

511

| | | |
|------|--------|--|
| 1353 | 0.0015 | |
| 1354 | 0.006 | |
| 1355 | 0.0015 | |
| 1356 | 0.22 | |
| 1357 | 0.023 | |
| 1358 | 0.008 | |
| 1359 | 0.014 | |
| 1360 | 0.003 | |
| 1361 | 0.004 | |
| 1362 | 0.019 | |
| 1363 | 0.008 | |
| 1364 | 0.006 | |
| 1365 | 0.008 | |
| 1366 | 0.015 | |
| 1367 | 0.002 | |
| 1368 | 0.005 | |
| 1369 | 0.005 | |
| 1370 | 0.002 | |
| 1371 | 0.004 | |
| 1372 | 0.004 | |
| 1373 | 0.008 | |
| 1374 | 0.007 | |
| 1375 | 0.002 | |
| 1449 | 0.052 | |
| 1450 | 0.039 | |
| 1451 | 0.014 | |

Additional *in vitro* taurocholate uptake tests and
in vivo rat gavage tests were conducted on the
following compounds listed in Tables 10 and 11.

SRL 6071
(C-3021/2)

512

TABLE 10
In Vitro Taurocholate Uptake
Assay Data for Some Additional Compounds
of the Present Invention

5

| Compound of Example Number | Human TC IC50 (nM) |
|----------------------------------|-----------------------|
| 1402 | 25 |
| 1403 | 23 |
| 1404 | 10 |
| 1405 | 21 |
| 1406 | 4 |
| 1407 | 3 |
| 1408 | 1 |
| 1409 | 0.9 |
| 1410 | 2 |
| 1411 | 2 |
| 1412 | 3 |
| 1413 | 3 |
| 1414 | 15 |
| 1415 | 2 |
| 1416 | 14 |
| 1417 | 2 |
| 1418 | <1 |
| 1419 | 3 |
| 1420 | 11 |
| 1421 | 4 |
| 1422 | 3 |
| 1423 | 3 |
| 1424 | 14 |
| 1425 | 2 |
| 1426 | 0.3 |
| 1427 | 2 |
| 1428 | 0.7 |
| 1429 | |
| 1430 | 3 |
| 1431 | 5 |
| 1432 | 26 |
| 1433 | 67 |

TABLE 11
Rat Gavage Assay Data for Some Additional Compounds
of the Present Invention

SRL 6071
(C-3021/2)

513

| Compound of Example No. | Study No. | Dose (mg/kg/day) | Delta (micromoles fecal bile acid per day) |
|----------------------------|-----------|---------------------|---|
| 1402 | 28 | 5 | 58.2 |
| | | .2 | 1.3 |
| | | .04 | 0.3 |
| 1402 | 30 | 2 | 50.3 |
| | | .4 | 40.9 |
| | | .08 | 48.5 |
| | | .016 | 22.9 |
| 1403 | 30 | 2 | 41.6 |
| | | .4 | 35.2 |
| | | .08 | 11.9 |
| | | .016 | 3 |
| 1404 | 28 | 5 | 93.7 |
| | | .2 | 59.1 |
| | | .04 | 33.5 |
| 1406 | 32 | 2 | 47.8 |
| | | .4 | 31.6 |
| | | .08 | 12.8 |
| | | .016 | -8.5 |
| 1407 | 32 | 2 | 51.9 |
| | | .4 | 30.1 |
| | | .08 | 27.5 |
| | | .016 | 6.4 |
| 1407 | 33 | 2 | 35 |
| | | .4 | 12.7 |
| | | .08 | -.04 |
| | | .016 | -4.5 |
| 1408 | 29 | 2 | 41.2 |
| | | .4 | 36.8 |
| | | .08 | 16.8 |
| | | .016 | -3.3 |
| 1408 | 37 | 2 | 26.2 |
| | | .4 | 45.2 |
| | | .08 | 26.3 |
| | | .016 | 6.6 |
| 1409 | 33 | 2 | 19.2 |
| | | .4 | 28.7 |
| | | .08 | 14.1 |
| | | .016 | -1.7 |
| 1409 | 41 | 2 | 44.2 |
| | | .4 | 35.9 |
| | | .08 | 14.5 |

SRL 6071
(C-3021/2)

514

| | | | |
|------|----|-----------------------------|------------------------------|
| | | .016 | 11 |
| 1410 | 33 | 32.4 34.3 27.9 9.3 | |
| 1410 | 35 | 2 .4 .08 .016 | 26.2 36.5 18.5 20.4 |
| 1411 | 34 | 2 .4 .08 .016 | 63.4 54.1 33 22.3 |
| 1413 | 26 | 5 .2 .04 | 52.3 42.4 19 |
| 1414 | 27 | 5 .2 .04 | 45.2 39.5 14.3 |
| 1414 | 31 | 2 .4 .08 .016 | 41.5 33.7 29 3.8 |
| 1415 | 28 | 5 .2 .04 | 59.9 48.1 23.9 |
| 1415 | 37 | 2 .4 .08 .016 | 48.9 25.7 27.1 12.7 |
| 1416 | 29 | 2 .4 .08 .016 | 46.1 21.9 25 -7.8 |
| 1417 | 31 | 2 .4 .08 .016 | 51.4 42 39.6 29.3 |
| 1418 | 29 | 2 .4 .08 .016 | 20.3 29.5 -4.6 -10 |
| 1419 | 31 | 2 .4 .08 .016 | 28.5 13.9 10.3 5.8 |
| 1420 | 31 | 2 .4 .08 .016 | 53.1 45 38.1 29.6 |
| 1421 | 32 | 2 | 57.8 |

SRL 6071
(C-3021/2)

515

| | | | |
|------|----|------------------------|------------------------------|
| | | .4 .08 .016 | 27.7 25.3 4.7 |
| 1423 | 34 | 2 .4 .08 .016 | 56.5 69.3 35.3 14.4 |
| 1425 | 21 | 5 .2 .04 | 91.8 100. 66.4 |
| 1425 | 30 | 2 .4 .08 .016 | 44.6 62 69.5 31.6 |
| 1425 | 40 | 2 .4 .08 .016 | 48.3 45 31.2 30 |
| 1426 | 33 | 2 .4 .08 .016 | 52.4 19.5 23.1 24.6 |
| 1426 | 35 | 2 .4 .08 .016 | 37.7 41.7 40.5 24.6 |
| 1426 | 39 | 2 .4 .08 .016 | 54.3 48.7 51.8 26.8 |
| 1426 | 43 | 2 .4 .08 .016 | 40.8 21.7 5.9 4.1 |
| 1427 | 40 | 2 .4 .08 .016 | 36.7 35.8 27.3 13.8 |
| 1428 | 34 | 2 .4 .08 .016 | 40.4 64.9 24.4 12.2 |
| 1428 | 42 | 2 .4 .08 .016 | 46 40.7 26 1.1 |
| 1429 | 41 | 2 .4 .08 | 34.5 24.9 18.7 |

SRL 6071
(C-3021/2)

516

| | | | |
|------|----|------|------|
| | | .016 | 9.2 |
| 1429 | 42 | 2 | 47.1 |
| | | .4 | 31.1 |
| | | .08 | 35.5 |
| | | .016 | 4.8 |
| 1430 | 30 | 2 | 51.2 |
| | | .4 | 50.4 |
| | | .08 | 20.7 |
| | | .016 | -5.6 |
| 1431 | 32 | 28.3 | |
| | | 45.8 | |
| | | 21.9 | |
| | | 1.1 | |
| 1432 | 28 | 5 | 36.2 |
| | | .2 | 9.7 |
| | | .04 | 2.4 |
| 1433 | 24 | 20 | 66.5 |
| | | 2 | 47.4 |
| | | .2 | 26.5 |

SRL 6071
(C-3021/2)

517

The examples herein can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

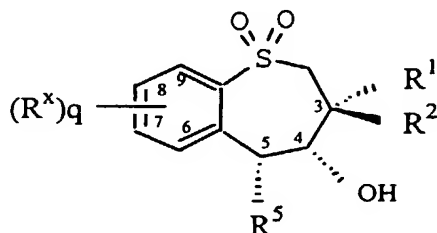
5 Novel compositions of the invention are further illustrated in attached Exhibits A and B.

10 The invention being thus described, it is apparent that the same can be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications and equivalents as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

SRL 6071
(C-3021/2)

518

Exhibit A
Table C2: Alternative Compounds #2 (Families F101-F123)



5

| Family | Cpd # | R ¹ =R ² | R ⁵ | (R ^x) q |
|--------|-------|--------------------------------|---|---------------------|
| F101 | | CHOSEN FROM TABLE 1 | Ph- | CHOSEN FROM TABLE 1 |
| F102 | | CHOSEN FROM TABLE 1 | p-F-Ph- | CHOSEN FROM TABLE 1 |
| F103 | | CHOSEN FROM TABLE 1 | m-F-Ph- | CHOSEN FROM TABLE 1 |
| F104 | | CHOSEN FROM TABLE 1 | p-CH ₃ O-Ph- | CHOSEN FROM TABLE 1 |
| F105 | | CHOSEN FROM TABLE 1 | m-CH ₃ O-Ph- | CHOSEN FROM TABLE 1 |
| F106 | | CHOSEN FROM TABLE 1 | p-(CH ₃) ₂ N-Ph- | CHOSEN FROM TABLE 1 |
| F107 | | CHOSEN FROM TABLE 1 | m-(CH ₃) ₂ N-Ph | CHOSEN FROM TABLE 1 |
| F108 | | CHOSEN FROM TABLE 1 | I ⁻ , p-(CH ₃) ₃ -N ⁺ -Ph- | CHOSEN FROM TABLE 1 |
| F109 | | CHOSEN FROM TABLE 1 | I ⁻ , m-(CH ₃) ₃ -N ⁺ -Ph- | CHOSEN FROM TABLE 1 |

SRL 6071
(C-3021/2)

519

| | | | | |
|------|--|---------------------------|--|---------------------------|
| F110 | | CHOSEN FROM TABLE 1 | $I^{-}, p-(CH_3)_3-N^{+}-CH_2CH_2-(OCH_2CH_2)_2-O-Ph-$ | CHOSEN FROM TABLE 1 |
| F111 | | CHOSEN FROM TABLE 1 | $I^{-}, m-(CH_3)_3-N^{+}-CH_2CH_2-(OCH_2CH_2)_2-O-Ph-$ | CHOSEN FROM TABLE 1 |
| F112 | | CHOSEN FROM TABLE 1 | $I^{-}, p-(N,N\text{-dimethylpiperazine})-(N')-CH_2-(OCH_2CH_2)_2-O-Ph-$ | CHOSEN FROM TABLE 1 |
| F113 | | CHOSEN FROM TABLE 1 | $I^{-}, m-(N,N\text{-dimethylpiperazine})-(N')-CH_2-(OCH_2CH_2)_2-O-Ph-$ | CHOSEN FROM TABLE 1 |
| F114 | | CHOSEN FROM TABLE 1 | $m-F-Ph-$ $p-CH_3O-$ | CHOSEN FROM TABLE 1 |
| F115 | | CHOSEN FROM TABLE 1 | 3,4,dioxy-methylene-Ph- | CHOSEN FROM TABLE 1 |
| F116 | | CHOSEN FROM TABLE 1 | $m-F-Ph-$ $p-F-Ph-$ | CHOSEN FROM TABLE 1 |
| F117 | | CHOSEN FROM TABLE 1 | $m-CH_3O-$ $p-F-Ph-$ | CHOSEN FROM TABLE 1 |
| F118 | | CHOSEN FROM TABLE 1 | 4-pyridine | CHOSEN FROM TABLE 1 |
| F119 | | CHOSEN FROM TABLE 1 | N-methyl-4-pyridinium | CHOSEN FROM TABLE 1 |
| F120 | | CHOSEN FROM TABLE 1 | 3-pyridine | CHOSEN FROM TABLE 1 |
| F121 | | CHOSEN FROM TABLE 1 | N-methyl-3-pyridinium | CHOSEN FROM TABLE 1 |

SRL 6071
(C-3021/2)

520

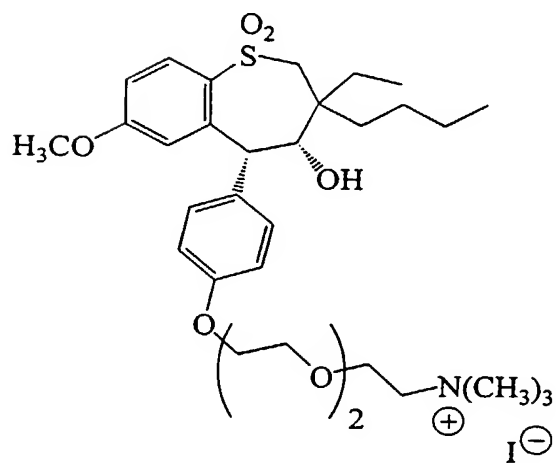
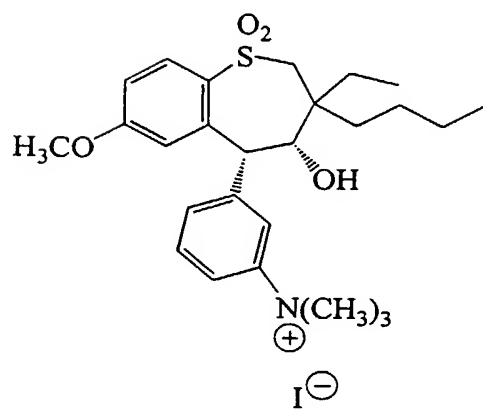
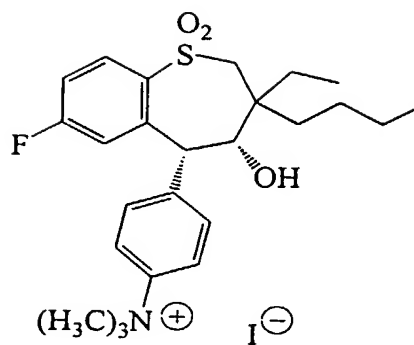
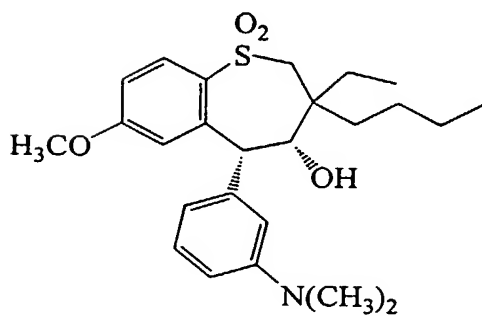
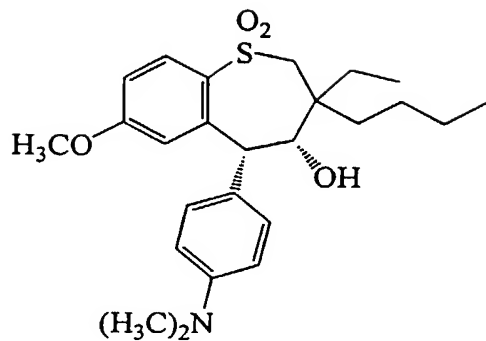
| | | | | |
|------|--|---------------------------|--|---------------------------|
| F122 | | CHOSEN FROM TABLE 1 | 2-pyridine | CHOSEN FROM TABLE 1 |
| F123 | | CHOSEN FROM TABLE 1 | p-CH ₃ O ₂ C-Ph- | CHOSEN FROM TABLE 1 |

Similar families can be generated where R¹ is not equal to R², such as R¹ = Et and R² = n-Bu, but (R^x)_q is chosen from table C1.

SRL 6071
(C-3021/2)

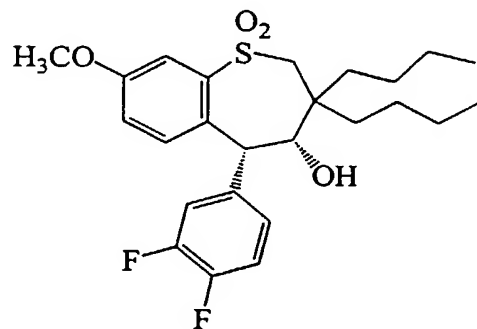
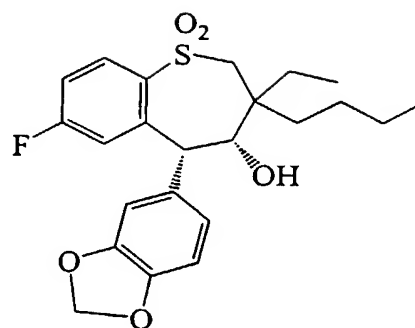
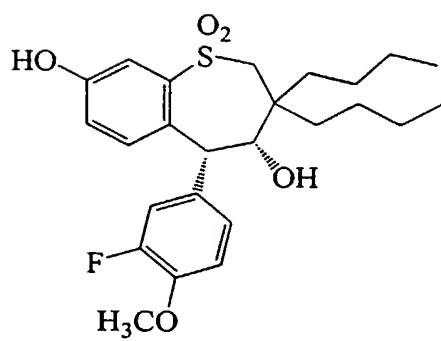
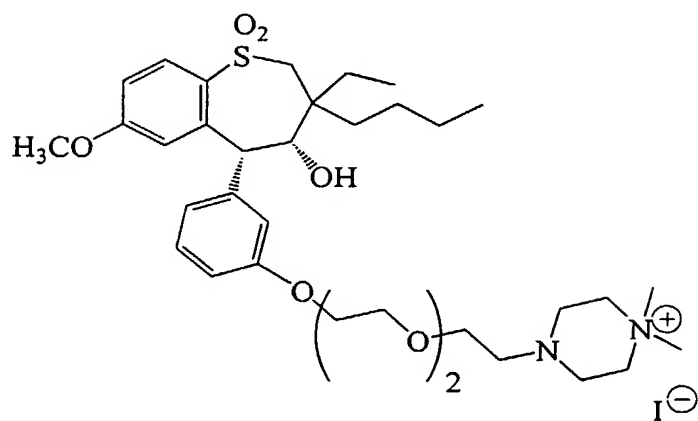
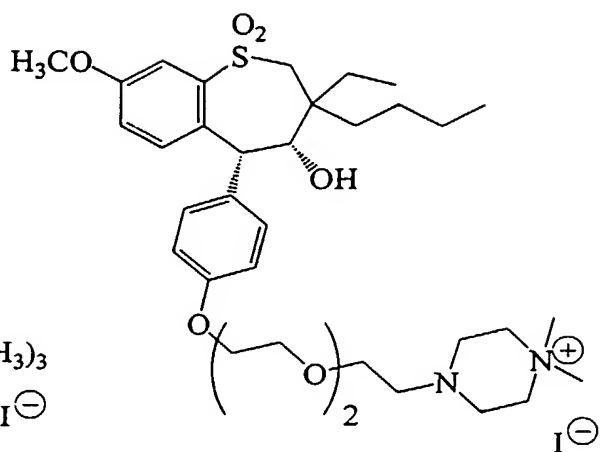
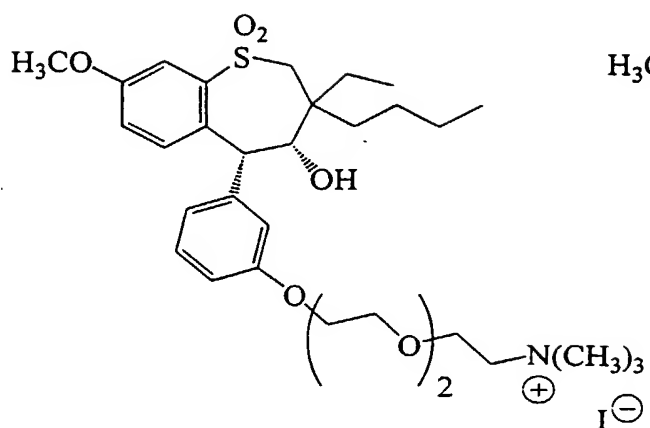
521

Exhibit B



SRL 6071
(C-3021/2)

522



SRL 6071
(C-3021/2)

523

